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American Heart Journal

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Original Communications

PULMONARY CIRCULATORY DYNAMICS IN MITRAL STENOSIS BEFORE AND AFTER COMMISSUROTOMY

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ONE IMPORTANT consequence of marked narrowing of the mitral orifice is increased blood pressure in the pulmonary circulation. This causes several of the most embarrassing symptoms in patients with rheumatic mitral stenosis. Surgical treatment, commissurotomy or valvuloplasty, also aims primarily at relieving the pulmonary hypertension and these symptoms by increasing the mitral valve opening.

In evaluating the results of such surgical intervention the most direct objective evidence for successful treatment is to what degree the pulmonary hypertension has been relieved. As it now is possible to measure exactly in man not only the pulmonary blood flow but also the pressures in the pulmonary circulation, it was considered worth while to study the pulmonary dynamics at rest and during exercise in patients with mitral stenosis before and after surgical treatment. The following is an account of such studies in thirty-nine cases investigated in Stockholm and Malmö and operated on by Crafoord (twenty-six cases) and Wulff (thirteen cases), respectively. Similar techniques have been used in all cases, both regarding the physiologic study and the surgical treatment.

METHODS

All patients were studied in the morning in the postabsorptive state. The pulmonary artery was catheterized according to Cournand.[1] The pulmonary capillary venous pressure[2] and the pulmonary and brachial arterial pressures were determined after thirty minutes of rest, almost simultaneously with the cardiac output according to Fick. In some cases, the same values were obtained again after at least eight minutes of slight work in the recumbent position.[3] The pressures were recorded together with electrocardiogram and Phonocardiogram with a Tybjaerg-Hansen electrical manometer.[4] The details of the procedure have been repeatedly described.[11]

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Similar studies have been performed in several centers.[5-11,17] We want to draw attention to the difficulty of performing such studies in severely sick patients in a way that makes it possible to draw conclusions from one patient to another or from one opportunity to another. This is not the place for a detailed criticism of methods used and we only want to point out some factors of importance for the evaluation of the results.

The determination of the cardiac output according to Fick requires simultaneous sampling of blood from the right side of the heart and a systemic artery and expired air. The patient must be in a steady and unchanging state during these procedures. This invalidates many of the figures published, especially those obtained during short bouts of exercise. Eliasch[11] recently showed that it is necessary to have at least a seven-minute period of exercise in patients with mitral stenosis before a steady state is reached.

The pressures in the pulmonary capillaries and the pulmonary artery should be registered without any interval and in close connection with the output determination.

In the present study, care has been taken to avoid such errors, and it is believed that errors of measurement are kept within a minimum, which notwithstanding that fact is rather large.

The pulmonary capillary venous pressure has been taken as representing the left auricular pressure. Data obtained in dogs and man indicate that there is a fair degree of correlation between these two, even when the left auricular pressure is elevated.[2,12-14]

Although the pulmonary hypertension reflects the degree of mitral valvular stenosis, determination of the pulmonary pressures only does not give an adequate basis for comparison of the state from one moment to another. Under the prevailing circumstances rather small changes in blood flow may give rather marked pressure changes both in the left auricle and the pulmonary artery. It is thus necessary to make a simultaneous determination of pressures and flow to be able to evaluate changes having taken place. Gorlin and Gorlin[15] have proposed a formula for the calculation of the size of the mitral orifice from such determinations. In our opinion too many unknown variables are incorporated in this calculation and we doubt that it is valid for that purpose. In this presentation we have instead calculated the total pulmonary resistance from the blood flow and the mean pressure of the pulmonary artery; the pulmonary vascular resistance from the difference of pressure in the PA and PCV and the mitral valvular resistance from the PCV and the blood flow.

$$\text{Pulmonary Vascular Resistance} = \text{P.V.R.} = \frac{(\text{P.A. mean-PCV mean}).\ \text{K}}{\text{C.O./sec.}}$$

$$\text{Total Pulmonary Resistance} = \text{T.P.R.} = \frac{\text{P.A. mean.}\ \text{K}}{\text{C.O./sec.}}.$$

P.A. = Pulmonary artery.
P.C.V. = Pulmonary capillary venous.
C.O. = Cardiac output.
K. = Constant factor.

Mitral Valvular Resistance = M.V.R. = T.P.R. − P.V.R. Resistance is thus calculated to dynes/sec./cm^{-5}.

These figures are only quotients of pressure over flow and roughly indicate how much of the pressure increase in the pulmonary artery is due to pulmonary vascular changes and how much is due to increased resistance in the stenosed valve opening. By using these calculations we have a means of objectively assessing the pulmonary circulation before and after operation and thus evaluating the results besides the patients' subjective feelings.

In all cases mitral commissurotomy was performed according to Bailey[16] or Baker and associates.[17] In most cases, only finger fracture was used but in some also the Bailey knife.

MATERIAL

Up to now forty-six cases have been operated upon. Of these seven patients have died, all in direct connection with the operation, which means a mortality rate of about 15 per cent. Patients with failure of the right side of the heart, active or recent endocarditis, and other valvular lesions besides the mitral stenosis have so far not been operated upon. Marked subjective symptoms and the desire of the patient to be operated upon have been the main indications. Of the thirty-nine surviving patients almost all have had subjective improvement, only slight in some cases but marked in others. In thirty-two of the survivors adequate studies have been performed before and two months after the operation, and the results in these studies together with the deceased form the basis for the following analysis.

RESULTS AND DISCUSSION

Figure 1 shows the mortality rate when the material is divided into three groups according to the severity of pulmonary hypertension. The high death rate in the group with most marked changes is demonstrated. In this group of ten cases with most marked changes of the pulmonary vascular dynamics six died and four improved markedly (Fig. 2). These cases had low output and excessively high pressures. One-half of them had auricular fibrillation and the heart size was markedly increased in some cases. In the middle group of sixteen cases (Fig. 3) mostly characterized by moderate increase in pressures and low blood flow or high pressures and normal blood flow, one died, three were not objectively better, and twelve cases improved. In this group only one third had fibrillation and the heart size was as a rule only moderately enlarged.

In the group of thirteen cases (Fig. 4) with less changes in the pulmonary circulation, usually almost normal output and moderately elevated pressures, no one died, but only five were clearly improved, while eight showed no significant change after the operation when studied at rest.

So far only the results of the basal studies have been discussed. In eleven cases adequate and complete studies of the pulmonary dynamics were obtained before and after the operation during the same degree of exercise in the recumbent position. The effect of exercise on pulmonary circulatory dynamics should be compared with that on the normal individual. Figure 5 shows representative

Fig. 1.

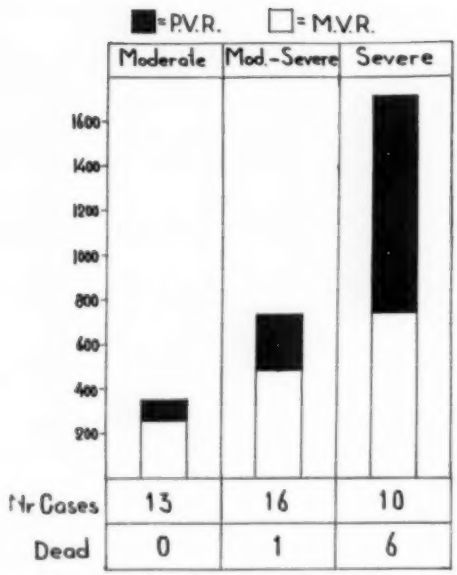
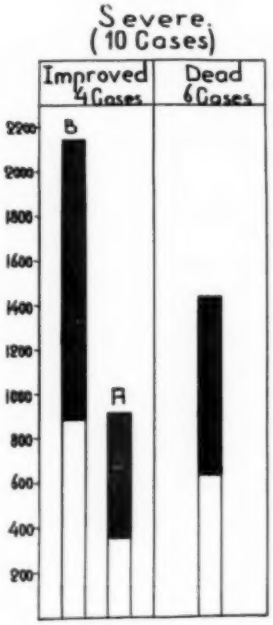


Fig. 2.



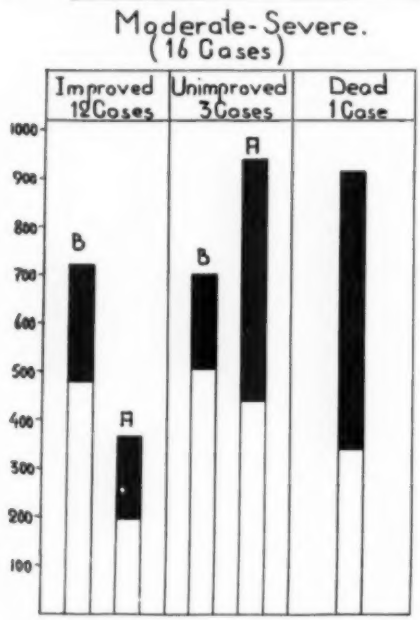


Fig. 3.

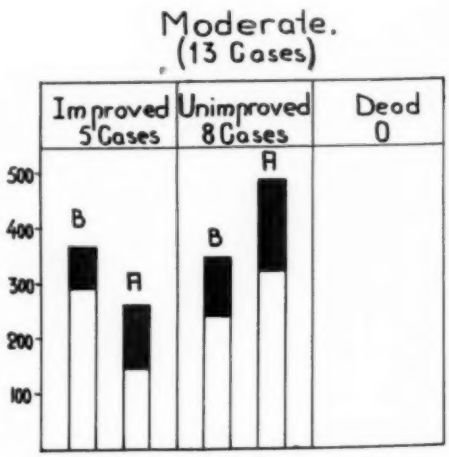


Fig. 4.

Fig. 1.—Graph showing the mortality rate after valvulotomy. The material is grouped according to the degree of pulmonary vascular resistances.

Fig. 2.—Graph showing results from valvulotomy in ten cases with severe pulmonary hypertension. *B* = before, *A* = after valvulotomy.

Fig. 3.—Graph showing results from valvulotomy in sixteen cases with moderately severe pulmonary hypertension. *B* = before, *A* = after valvulotomy.

Fig. 4.—Graph showing results from valvulotomy in thirteen cases with moderate pulmonary hypertension. *B* = before, *A* = after valvulotomy.

TABLE IZ. PRESSURE IN MM.HG AND FLOW IN THIRTEEN CASES WITH MODERATE PULMONARY HYPERTENSION

CASE NR.	SEX	AGE	B.S.A. m^2	RHYTHM	HEART VOL. ml/m^2 B.S.A.	PULSE RATE	A-V O_2DIFF. ml/l	CARDIAC IND. l/min./m^2	PULM. ART. PRESS.			PCV PRESS.	BRACH. ART. PRESS.			R. AUR. PRESS.	P.V.R.	T.P.R.
									S	D	M	M	S	D	M	M		
281	F	38	1.80	A.F.	720	60	49	2.1	32	14	21	17	105	62	78	4	84	442
295			1.77	A.F.	830	100	56	2.7	55	34	42	29	125	88	100	5	217	700
315	F	39	1.55	S	575	100	52	3.4	39	18	28	22	124	82	98	1	93	432
340			1.37	S	500	98	38	6.3	45	22	29	21	147	94	115	2	74	269
337	F	44	1.66	S	470	76	46	2.8	33	15	21	19	129	77	100	4	35	364
369			1.62	S	470	92	42	3.7	28	9	17	10	131	76	98	0	94	229
354	F	45	1.64	S	390	65	40	2.6	33	11	19	16	123	78	94	3	55	350
376			1.76	S	480	67	44	2.8	40	20	27	17	137	89	103	—	162	437
380	M	46	1.86	A.F.	590	66	54	2.1	30	15	20	12	148	90	108	0	163	408
415			1.81	A.F.	430	76	52	2.3	31	18	23	13	—	—	—	2	193	443
388	F	30	1.52	S	560	82	32	4.9	50	25	36	25	114	78	88	0	119	390
452			1.57	S	560	75	28	5.1	38	22	28	14	107	65	81	4	138	277
392	F	26	1.58	S	410	120	29	5.1	36	16	23	14	122	74	92	1	89	229
418			1.54	S	410	108	41	4.3	28	16	20	13	118	79	95	1	89	237
397	F	43	1.69	A.F.	520	86	43	3.2	35	19	25	21	108	59	74	2	60	375
456			1.64	S	520	76	40	3.9	32	13	19	10	97	52	70	1	114	240
424	F	31	1.71	S	680	71	50	3.4	29	18	22	18	127	82	102	0	55	300
479			1.74	S	500	79	63	2.1	23	11	15	14	124	75	95	3	22	323
462	F	43	1.78	S	430	120	25	5.6	48	25	35	23	127	83	100	0	95	280
497			1.77	S	360	118	36	4.9	30	21	28	13	128	63	89	—	139	260
M_7	M	41	1.88	S	590	63	42	2.5	45	20	28	16	—	—	—	1	204	476
			1.81	S	545	63	50	2.2	45	15	31	18	—	—	—	4	258	617
M_8	F	41	1.82	S	550	86	37	2.8	20	12	16	10	—	—	—	0	94	251
			1.82	S	450	86	58	2.1	33	18	24	17	—	—	—	−2	147	505
M_9	F	35	1.72	S	595	70	35	3.7	43	21	24	18	—	—	—	3	76	305
			1.71	S	515	70	47	2.4	38	15	24	18	—	—	—	5	118	473

S = systolic, D = diastolic, M = mean. In each column upper case nr. is before, lower case nr. after valvulotomy. P.V.R. = pulmonary vascular resistance in dynes/sec./cm.$^{-5}$ T.P.R. = total pulmonary resistance in dynes/sec./cm.$^{-5}$ B.S.A.m^2 = body surface area in m^2.

TABLE IB. PRESSURE IN mm.Hg AND FLOW IN SIXTEEN CASES WITH MODERATELY SEVERE PULMONARY HYPERTENSION

CASE NR.	SEX	AGE	B.S.A. m^2	RHYTHM	HEART VOL. ml/m^2 B.S.A.	PULSE RATE	A-V O_2DIFF. ml/l	CARDIAC INDEX l/min./m^2	PULM. ART. PRESS.			PCV PRESS.	BRACH. ART. PRESS.			R. AUR. PRESS.	P.V.R.	T.P.R.
									S	D	M	M	S	D	M	M		
292	F	31	1.71	S	680	76	57	2.7	63	37	47	24	110	62	80	3	398	805
321			1.64	S	680	78	45	3.0	35	15	24	14	135	75	97	3	161	385
297	F	36	1.57	S	770	116	40	4.2	95	43	69	37	103	65	78	4	388	837
329			1.55	S	770	97	35	4.9	35	18	25	4	119	78	93	1	221	329
309	M	43	1.79	S	620	107	56	3.0	97	43	65	34	101	77	88	3	468	980
331			1.76	S	510	67	42	3.9	33	12	20	10	121	78	97	2	106	231
316	M	38	1.81	S	620	78	51	2.8	63	29	41	25	134	89	103	3	251	644
350			1.75	S	640	68	44	3.6	42	14	23	11	141	99	115	1	151	342
334	F	39	1.59	S	480	72	50	2.5	45	25	32	21	128	85	104	1	222	645
490			1.58	S	530	82	28	4.9	33	14	23	16	123	82	99	4	73	239
358 +	F	42	1.58	S	590	90	47	3.3	93	42	59	22	140	94	112	2	576	918
360	F	40	1.58	A.F	630	80	49	2.7	51	30	39	29	182	134	155	1	188	734
379			1.56	A.F	650	84	58	2.4	47	29	34	24	—	—	—	5	210	714

403 499	M	45	1.62 1.55	S S	420 420	63 77	47 37	2.9 4.6	48 62	23 28	32 38	28 23	120 99	72 65	90 75	2 2	67 168	536 423
436 488	F	33	1.40 1.40	S S	510 510	107 112	36 32	4.2 4.4	65 46	33 19	42 28	22 14	109 121	62 70	85 89	−1 1	271 194	570 376
464 496	F	40	1.62 1.61	A.F S	480 480	95 86	47 39	2.4 3.2	64 50	39 23	47 30	23 8	123 91	81 46	100 62	4 −2	490 337	960 460
476 513	F	34	1.52 1.47	S S	440 450	78 109	43 53	2.6 2.1	46 54	22 24	30 40	15 15	123 114	71 86	82 101	4 −1	307 647	615 1035
M_2	F	30	1.43 1.40	S S	500 500	54 86	47 37	2.1 3.0	48 42	20 19	30 29	19 18	— —	— —	— —	6 3	287 207	784 547
M_3	F	44	1.56 1.53	A.F A.F	735 715	52 80	50 50	2.3 2.4	43 67	21 38	33 49	30 27	— —	— —	— —	2 7	68 475	746 1059
M_4	F	44	1.81 1.85	S S	570 555	70 75	42 43	2.8 2.4	74 49	23 21	51 31	39 14	— —	— —	— —	2 2	192 309	816 564
M_5	F	25	1.72 1.73	A.F A.F	980 730	60 48	49 47	2.3 2.4	35 15	17 10	25 12	25 12	— —	— —	— —	3 3	20 0	525 232
M_6	F	33	1.59 1.60	S S	550 530	86 86	59 37	2.3 3.4	34 35	20 15	25 27	25 16	— —	— —	— —	2 3	22 160	578 393

S = systolic, D = diastolic, M = mean. In each column upper case nr. is before, lower case nr. after valvulotomy. P.V.R. = pulmonary vascular resistance in dynes/sec./cm.$^{-5}$ T.P.R. = total pulmonary resistance in dynes/sec./cm.$^{-5}$ + = died after operation. B.S.A.m^2 = body surface area in m^2.

TABLE IC. PRESSURE IN mm.Hg AND FLOW IN TEN CASES WITH SEVERE PULMONARY HYPERTENSION

CASE NR.	SEX	AGE	B.S.A. m^2	RHYTHM	HEART VOL. ml/m^2 B.S.A.	PULSE RATE	A-V O_2DIFF. ml/l	CARDIAC INDEX l/min./m^2	PULM. ART. PRESS.			PCV PRESS.	BRACH. ART. PRESS.			R. AUR. PRESS.	P.V.R.	T.P.R.
									S	D	M	M	S	D	M	M		
306	F	41	1.47	S	565	78	55	2.6	87	41	58	25	118	77	93	3	575	1190
320			1.42	S	570	71	44	3.1	44	19	30	13	132	84	103	2	312	549
367 +	F	46	1.47	S	630	109	60	2.5	128	65	88	25	133	98	110	2	1350	1887
373 +	F	40	1.44	A.F	810	70	66	1.4	69	31	42	19	125	83	95	5	893	1631
402 +	M	45	1.56	A.F	720	80	62	2.1	62	37	47	27	112	70	87	1	490	1150
408	F	41	1.43	S	400	120	56	2.3	132	87	109	40	110	73	84	3	1710	2700
481			1.43	S	500	125	32	4.2	78	43	52	15	120	75	93	−1	498	700
M_1	F	24	1.37	S	805	100	75	1.6	104	58	73	31	—	—	—	10	1530	2654
			1.37	S	525	80	61	1.9	61	31	41	17	—	—	—	2	738	1261
M_{10}	F	37	1.34	S	555	100	60	2.1	103	54	42	32	—	—	—	2	1143	2057
			1.32	S	520	71	38	3.0	70	33	48	16	—	—	—	2	640	960
M_{11} +	F	51	1.63	S	645	57	65	1.6	53	24	33	12	—	—	—	2	651	1023
M_{12} +	F	45	1.77	A.F	610	67	108	1.0	55	25	33	18	—	—	—	2	705	1553
M_{13} +	M	37	1.70	A.F	1280	54	70	1.8	68	31	44	—	—	—	—	10	—	1173

S = systolic, D = diastolic, M = mean. In each column upper case nr. is before, lower case nr. after valvulotomy. P.V.R. = pulmonary vascular resistance in dynes/sec./cm.$^{-5}$ T.P.R. = total pulmonary resistance in dynes/sec./cm.$^{-5}$ + = died after operation. B.S.A.m^2 = body surface area in m^2.

results from such a study in a normal medical student. The pulmonary resistances decrease concomitant with the increase in cardiac output. In mitral stenosis, on the contrary, both the total pulmonary resistance and the mitral valvular resistance invariably increased already with slight effort. Figure 6 compares the reaction to exercise before and after operation and demonstrates a definite decrease in the mitral valvular resistance during exercise in accordance with the findings under resting conditions. In some cases, the pulmonary vascular resistance increased after operation; in a few cases increased resistance could be correlated to pulmonary embolism or atelectasis or to fairly long-standing pleural exudation after operation. This alteration may be of short duration and does not necessarily cause permanent increase of the pulmonary hypertension.

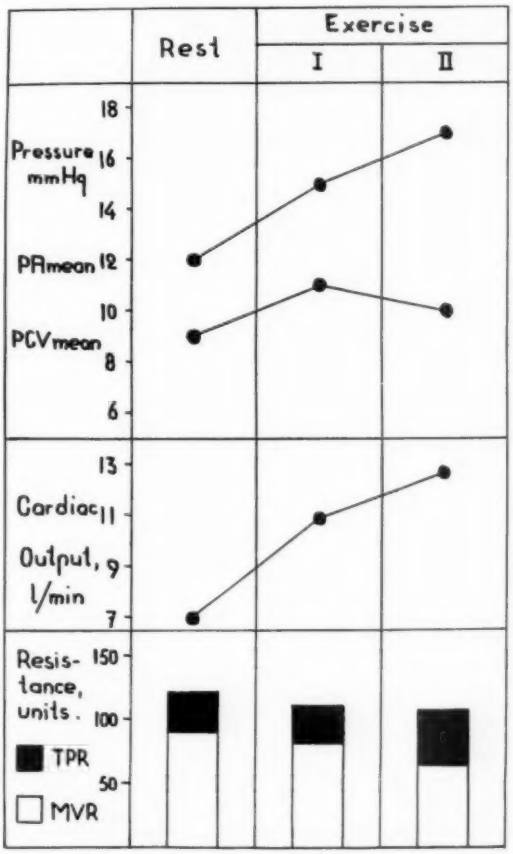


Fig. 5.—Graph showing the response to exercise on the pulmonary circulation in a normal medical student. Exercise I: work load = 70 kgm/min.; exercise II: work load = 250 kgm/min.

Figure 7 shows the results of studies during exercise in some cases where the resting values were unchanged. In two of these cases, there was slight improvement by the values obtained during exercise.

In no case did the pulmonary dynamics return to normal after operation. Although the improvement in several cases was remarkable, there always re-

mained a pathologic reaction to exercise typical for mitral stenosis, even in the most successful cases. This fact is of importance for the discussion of the indications for commissurotomy in cases with only slight changes.

From these results, it is obvious that there is a middle group of cases, with marked but not too advanced stage of disease, where the operative mortality is low and signs of objective improvement are present in a large number of cases. How are these findings related to the results of easier and more ordinary clinical investigations in these patients?

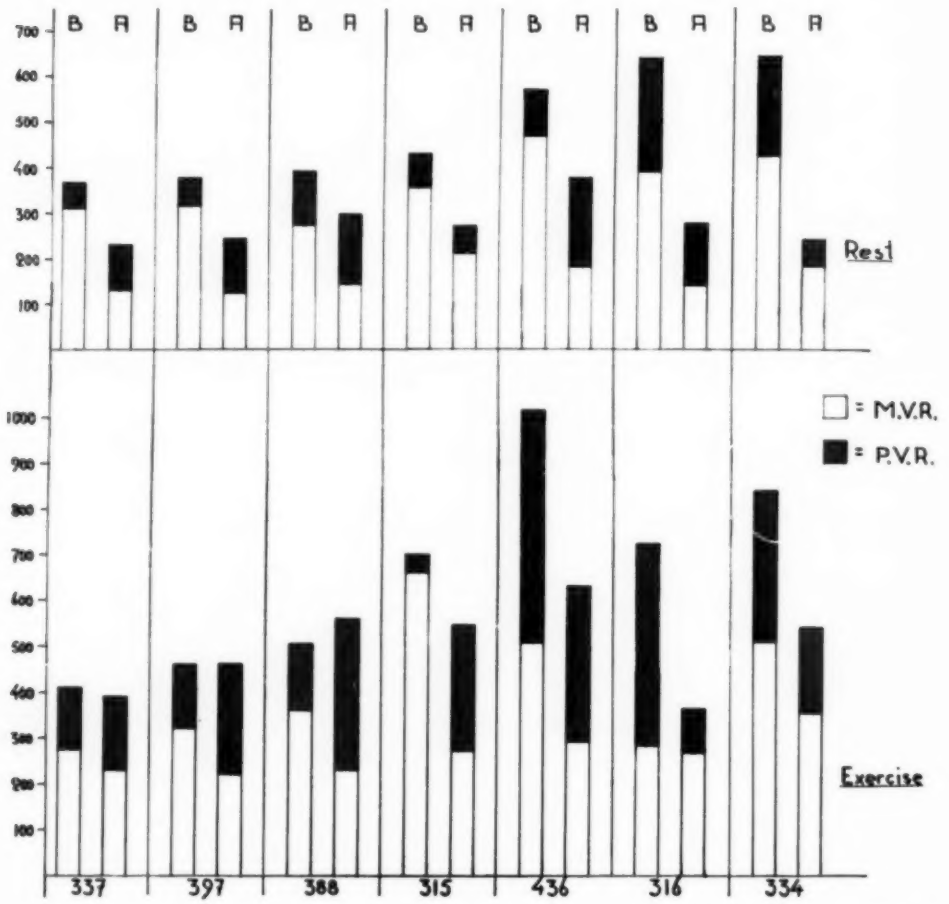


Fig. 6.—Graph showing changes in pulmonary resistances before *B* and after *A* valvulotomy, obtained at rest and during exercise (70 kgm/min.) in seven cases of mitral stenosis.

Of the thirty-nine cases, fourteen had auricular fibrillation. Of these five died, and four were unchanged. Only one-third showed objective signs of improvement. Of the twenty-five cases with sinus rhythm two died and four were unchanged while three-fourths were improved.

The influence of age is shown in Fig. 8. It is seen that even in the age group 41 to 45 years there are seven cases improved, with three deaths and four un-

changed, that is improvement in 50 per cent of the cases. Above the age of 45 no one improved. No deaths occurred in the cases below 35 years of age.

The heart size was calculated according to the formula of Liljestrand and associates in all cases.[18] Increased size of the left auricle alone gives marked increase in this calculation. Figure 9 shows the cases grouped according to the roentgenologic heart size. The best results were obtained in cases with heart size below 600 ml/m² B.S.A. Above this figure only five cases improved against six deaths and three unimproved.

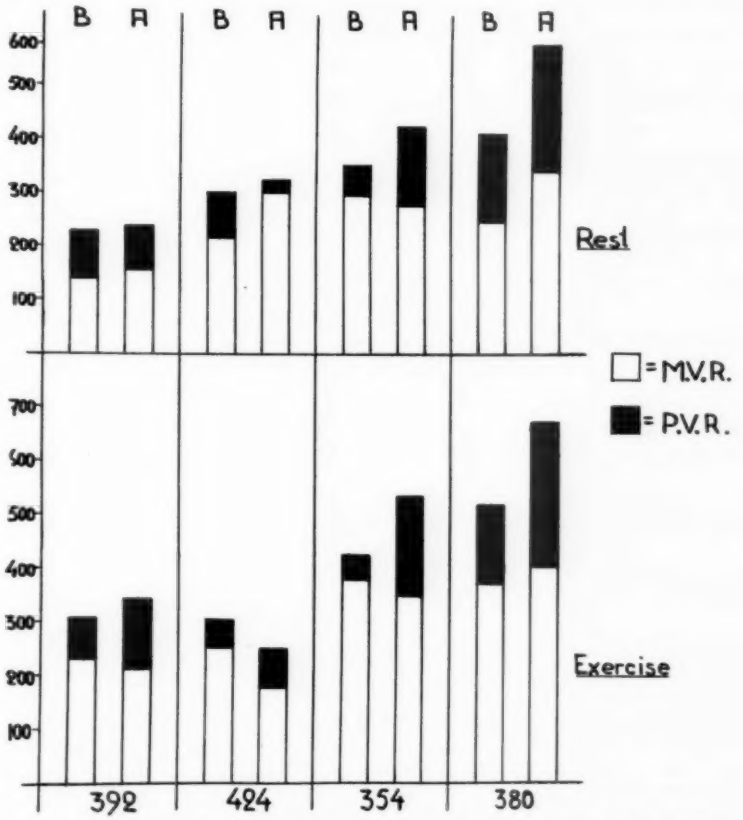


Fig. 7.—Graph showing changes in pulmonary resistances before *B* and after *A* valvulotomy, obtained at rest and during exercise (70 kgm/min.). In these four cases resting values were essentially unaffected by operation.

Figure 10 is obtained by taking age, rhythm, and heart size simultaneously into consideration. The best objective result judged from the dynamics of the pulmonary circulation was obtained in the present series in cases below the age of 45, with sinus rhythm and heart size less than 600 ml/m² B.S.A. (only slightly enlarged) and symptoms corresponding to Group III or IV of the New York Heart Association.[19]

The observations in the cases with only moderate alteration of the pulmonary dynamics have to be especially stressed. In this group there was no mortality but the percentage of cases improved was smaller than in any other

group. Almost one-half of the cases showed no improvement in pulmonary circulatory dynamics after commissurotomy. Several had increased pulmonary vascular changes after the operation probably due to complications in the postoperative course, which was of special importance for the net result of the operation as the changes to start with were not so marked.

A large number of the cases with mitral stenosis that we have studied have had almost normal circulatory dynamics at rest. There is reason to believe that many or all of these cases may live a normal life span. Also it should be stressed that even if the immediate postoperative result is excellent, nobody knows how long the improvement of the circulation may last. From our experience there does not seem to exist any real support for the attempt to use the operation as a prophylactic measure in the early phase of the disease.

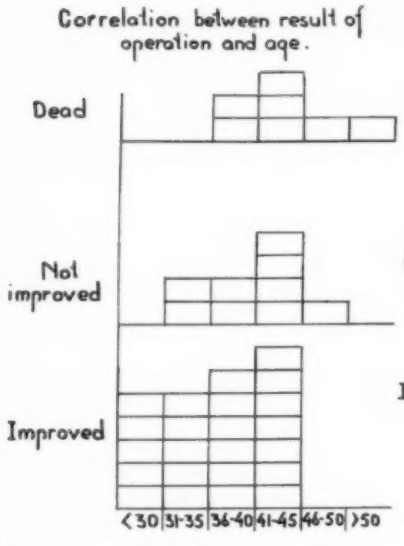


Fig. 8.

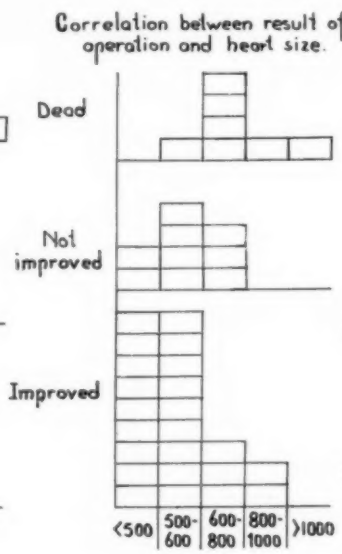


Fig. 9.

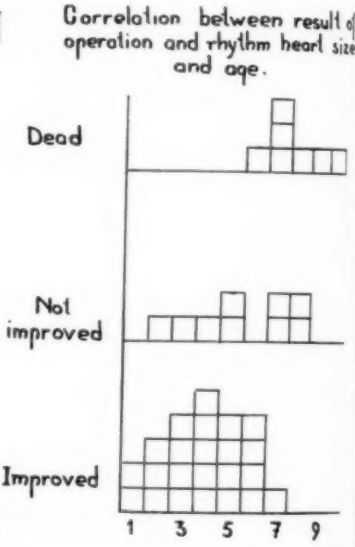


Fig. 10.

Fig. 8.—Graph showing the relationship between age and the operative results.

Fig. 9.—Graph showing the relationship between the roentgenologic heart size and the operative results.

Fig. 10.—Graph showing the relationship between heart rhythm, roentgenologic heart size, age, and the operative results.

Calculation of points:	
Sinus rhythm	1
Fibrillation	3
Age below 30	0
31-35	1
36-40	2
41-45	3
46-50	4
above 50	5
Heart size below 500	0
ml/m²BSA. 500- 600	1
600- 800	2
800-1000	3
above 1000	4

The new era of surgical treatment of mitral stenosis has brought beneficial results to a large group of patients. Naturally this has caused a growing enthusiasm both from our surgical colleagues and from the large body of patients suffering from different heart diseases. It is most important, therefore, that the indications and contraindications for surgical treatment are clearly defined, not only from theoretical considerations but from actual results gained by the procedure. The present study aims at such a goal. So far the series is small and the results only preliminary. Nevertheless the observations made constitute a suggestive basis for more firmly founded indications and contraindications for commissurotomy. The material will eventually be enlarged and give more exact information to this end.

SUMMARY

1. Forty-six cases of mitral stenosis were operated upon by digital commissurotomy. No case was in right heart failure. No other valvular lesions of important degree were demonstrated. Seven cases died in direct connection with the operation.

2. All cases were studied with the heart catheterization technique before and about six weeks after operation. The response to slight, graded work was also studied before and after valvulotomy in eleven cases.

3. The best objective results from operation were obtained in cases below the age of 45 years, with sinus rhythm and heart size less than 600 ml/m² B.S.A. and symptoms corresponding to Group III or IV.

4. Commissurotomy has afforded beneficial results to many cases of mitral stenosis, suggesting further operative treatment of this disease. Thorough hemodynamic studies are still needed to form proper indications and contraindications.

After this paper was submitted for publication F. A. Rodrigo made a critical study of the methods of estimating the mitral valve area according to Gorlin and Gorlin and valvular resistance using a similar index as in the present paper. (Am. Heart J. **45**:1, 1953). Rodrigo prefers to use the Gorlin formula, but supposes that the blood flow is constant through the mitral valve and that the pcv mean pressure represents the pressure head during diastole, both of which are erroneous.

REFERENCES

1. Cournand, A.: Recent Observations on the Dynamics of the Pulmonary Circulation, Bull. New York Acad. Med. **23**:27, 1947.
2. Lagerlöf, H., and Werkö, L.: Studies on the Circulation of Blood in Man. VI. The Pulmonary Capillary Venous Pressure Pulse in Man, Scandinav. J. Clin. & Lab. Invest. **1**:147, 1949.
3. Eliasch, H., Wade, G., and Werkö, L.: The Effects of Work on the Pulmonary Circulation in Mitral Stenosis, Circulation **5**:271, 1952.
4. Hansen, A. Tybjaerg: Pressure Measurements in the Human Organism, Copenhagen, 1949, Teknisk Forlag.
5. Gorlin, R., Sawyer, C. G., Haynes, F. W., Goodale, W. T., and Dexter, L.: Effects of Exercise on Circulatory Dynamics in Mitral Stenosis. III. AM. HEART J. **41**:192, 1951.
6. Harken, D. E., Ellis, L. B., Ware, P. F., and Norman, L. R.: The Surgical Treatment of Mitral Stenosis, New England J. Med. **239**:801, 1948.
7. Draper, A., Heimbecker, R., Daley, R., Carroll, D., Mudd, G., Wells, R., Falholt, W., Andrus, E. C., and Bing, R. J.: Physiologic Studies in Mitral Valvular Disease, Circulation **3**:531, 1951.

8. Bayliss, R. I. S., Etheridge, M. J., and Hyman, A. L.: Pulmonary Hypertension in Mitral Stenosis, Lancet **2**:889, 1950.
9. Cournand, A., Lequime, J., and Reguiers, P.: Analyse physiologique des facteurs et des symptomes de l'insuffisance circulatoire chronique, Acta Cardiol. **6**:343, 1951.
10. (a) Ellis, L. B., Bloomfield, R. A., Graham, G. K., Greenberg, D. J., Hultgren, H. N., Kraus, H., Maresh, G., Mebane, J. G., Pfeiffer, P. H., Selverstone, L. A., and Taylor, J. A.: Studies in Mitral Stenosis. I. A Correlation of Physiologic and Clinical Findings, Arch. Int. Med. **88**:515, 1951.
(b) Soulié, P., Carlotti, J., Sicot, J. R., and Joly, F.: Étude hémodynamique du rétrécissement mitral, Semaine hop. Paris **50**: Septembre 1951.
(c) Baker, C., Brock, R. C., Campbell, M., and Wood, P.: Valvulotomy for Mitral Stenosis, Brit. M. J. **1**:1043, 1952.
(d) Werkö, L., Eliasch, H., Berglund, F., and Crafoord, C.: Circulatory Studies in Mitral Stenosis Before and After Commissurotomy, Ann. Surg. **135**:290, 1952.
(e) Wulff, H. B., Biörck, G., Bergh, N. P., Krook, H., Axéa, O., and Lundskog, O.: Studies in Mitral Stenosis. I. Results of One Year's Surgical Treatment of Mitral Stenosis, Acta Med. Scandinav. In press.
(f) Biörck, G., Axén, O., Krook, H., Andrén, L., and Wulff, H. B.: Studies in Mitral Stenosis. IV. The Relative Merits of Various Diagnostic Methods in Mitral Valvular Disease, Am. Heart J. **45**:13, 1953.
11. Eliasch, H.: The Pulmonary Circulation at Rest and on Effort in Mitral Stenosis, Scandinav. J. Clin. Lab. Invest. **4**: (suppl. 4,) 1952.
12. Hellems, H. K., Haynes, F. W., and Dexter, L.: Pulmonary "Capillary" Pressure in Man, J. Appl. Physiol. **2**:24, 1949.
13. Dow, J. W., and Gorlin, R.: Pulmonary Capillary Pressure as an Index of Left Auricular Mean Pressure in Dogs, Federation Proc. **9**:33, 1950.
14. Werkö, L., and Lagerlöf, H.: The Pulmonary Capillary Venous Pressure in Man, Paris, 1950, Resumés Prem. Congrés. mond. Card. Baillière, 144.
15. Gorlin, R., and Gorlin, S. G.: Hydraulic Formula for Calculation of the Area of the Stenotic Mitral Valve, Other Cardiac Valves and Central Circulatory Shunts. I., Am. Heart J. **41**:1, 1951.
16. Bailey, C. P.: The Surgical Treatment of Mitral Stenosis (Mitral Commissurotomy), Dis. of Chest. **15**:377, 1949.
17. Baker, C., Brock, R. C., and Campbell, M.: Valvulotomy for Mitral Stenosis: Report of 6 Successful Cases, Brit. M. J. **1**:1283, 1950.
18. Liljestrand, G., Lysholm, E., Nylin, G., and Zachrison, C. G.: The Normal Heart Volume in Man, Am. Heart J. **17**:406, 1939.
19. Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart. Ed. IV. 1945. New York: New York Heart Association Inc.

SUBENDOCARDIAL TRAUMA PRODUCED BY RIGHT-SIDED CATHETERIZATION OF THE HEART IN MAN

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TWO RECENT reports have summarized the literature regarding the endocardial damage[7] produced by venous catheterization of the heart, and the arrhythmias which may result from catheterization.[3,7] Among catheterized patients brought to post-mortem examination, Johnson and associates[6] and Holling and Zak[5] have reported the presence of intracardiac thrombi one month and ten days, respectively, after catheterization. Zimdahl alone has reported an arrhythmia lasting more than twelve hours.[7] In his case, that of a four-year-old boy with the Tetralogy of Fallot, complete auriculoventricular block was noted on the morning following passage of the catheter. The arrhythmia retrogressed spontaneously through the stages of second and first degree heart block until a sinus rhythm became re-established on the seventh day. Zimdahl postulated that the bundle of His may have been injured by the occurrence of a small subendocardial hemorrhage. The production of the latter in dogs, together with mural thrombosis and subjacent myocardial necrosis, was described by Banfield and associates[1] and Ellis and co-workers;[2] in addition, Goodale and associates[4] demonstrated the healed end result of subendocardial fibrosis in dogs permitted to survive several weeks after intracardiac manipulation of the catheter.

We report here one case of subendocardial hemorrhages and one of right bundle branch block of five days' duration, both resulting from cardiac catheterization.

CASE REPORTS

CASE 1.—E. H., a 39-year-old Negro woman, was catheterized on Dec. 7, 1950, for the purpose of investigation of the hemodynamic changes incidental to the administration of high spinal anesthesia. A fairly flexible No. 6F catheter was introduced slowly and without meeting obstruction into the right atrium. On the first attempt to enter the tricuspid orifice, the tip of the catheter impinged high on the lateral wall of the right atrium and was partially withdrawn. Following manipulation of the catheter, the tip was oriented medially and introduced in one movement into the right ventricle. On the third attempt, the pulmonary artery was entered and the tip permitted to remain proximally in the left pulmonary artery. Following intratracheal intubation, cholecystectomy was performed under Pentothal Sodium and procaine high spinal anesthesia. Mid-

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way through the surgical procedure, positive pressure artificial respiration was necessary for 30 minutes. Arterial blood specimens were not obtained at this time, although prior to this period collection for the determination of cardiac output revealed an arterial saturation of 96 per cent. The procedure was terminated at 1:40 P.M., four hours after introduction of the catheter. The patient expired suddenly 28 hours later.

At *post-mortem examination* death was attributed to massive atelectasis of the left lung and focal atelectasis of the right lung. Petechial subintimal hemorrhages were found in the right subclavian and innominate veins and in the superior vena cava. In the right atrium, on the anterolateral wall, there was a circular, solitary bright red subendocardial hemorrhage, which exactly matched the tip of the catheter used. Similar foci, about 0.4 by 0.1 cm. in diameter, were noted in the right ventricle posteriorly near the base, and in the substance of the posterior cusp of the pulmonic valve (Fig. 1). Microscopic examination revealed small subendocardial collections of erythrocytes without evidence of myocardial damage. No other such areas were noted, nor were petechiae seen elsewhere in the thoracic, abdominal, and cranial viscera.

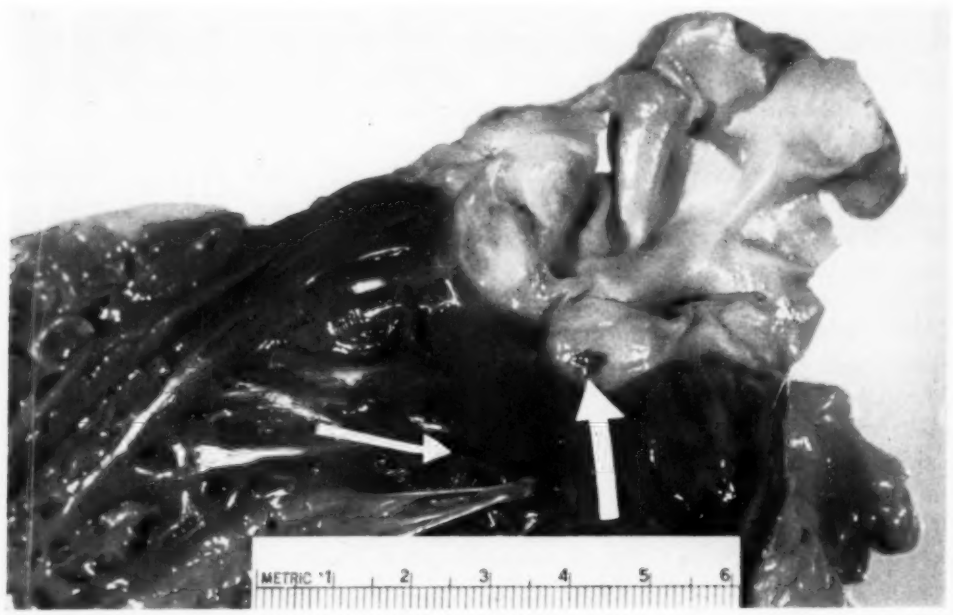

FIG. 1.—(Case 1) Right ventricular aspect of interventricular septum and pulmonary artery; arrows indicate petechiae.

CASE 2.—L. H., a Negro woman, aged 59 years, was catheterized on May 10, 1951, for investigation of the effects of high spinal anesthesia during surgery. A No. 7F catheter was introduced without difficulty into the right ventricle. On the first attempt to enter the pulmonary artery, the tip of the catheter impinged high against the medial aspect of the right ventricle. The monitored cardioscope immediately exhibited prolonged interventricular conduction time (Lead II). The catheter was withdrawn into the right atrium, and a 12 lead electrocardiogram was taken, showing a right bundle branch block. Similar daily electrocardiograms were recorded until May 16, 1951, when spontaneous reversion to the previously normal conduction was inscribed (Fig. 2).

DISCUSSION AND CONCLUSIONS

The subintimal and subendocardial hemorrhages described in the first case were caused by the trauma of the catheter. Whether these lesions would have developed in the absence of a transient anoxia which may have occurred during

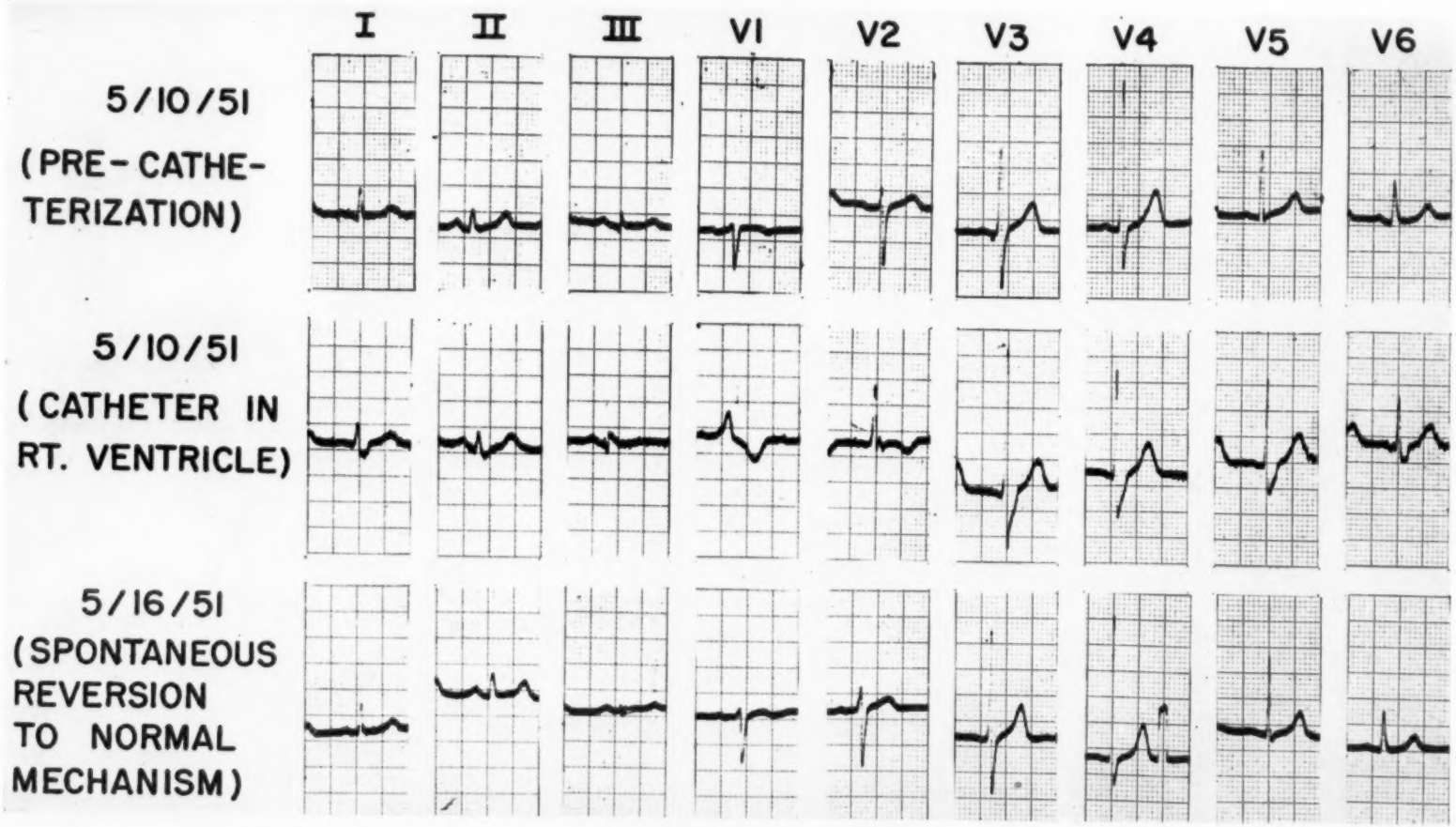

Fig. 2.—(Case 2) Electrocardiogams showing normal mechanism, right bundle branch block, and reversion to a normal mechanism five days later.

operation is unknown, although they were noted only in areas traumatized by the catheter. There was no known disturbance in the clotting mechanism of this patient. In the second case one may infer, as did Zimdahl,[7] that a subendocardial hemorrhage in the region of the bundle may have been responsible for the right bundle branch block which persisted for five days after catheterization. Electrocardiograms recorded on this patient two and four weeks later showed persistence of a normal conduction. In neither case was there evidence of heart disease.

That subendocardial hemorrhages may occur as the result of cardiac catheterization in man is demonstrated in Case 1. As one may judge, they are probably uncommon, and of importance only in that they may possibly be responsible for an occasional case of persistent conduction defect following cardiac catheterization.

REFERENCES

1. Banfield, W. G., Hackel, D. B., and Goodale, W.: Cardiac Lesions Following Venous Catheterization of the Right Auricle and Coronary Sinus of Dogs, J. Lab. & Clin. Med. **35**:287, 1950.
2. Ellis, F. J., Essex, H. E., and Edwards, J. E.: Lesions of the Heart in Dogs Following Cardiac Catheterization, Proc. Staff Meet., Mayo Clin. **25**:73, 1950.
3. Fowler, N. O., Westcott, R. N., and Scott, R. C.: Disturbances in Cardiac Mechanism of Several Hours' Duration Complicating Cardiac Venous Catheterization, Am. Heart J. **42**:652, 1951.
4. Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., Durlacher, S. H., Lauding, B. H., and Banfield, W. G.: Coronary Sinus Catheterization Technique for Studying Coronary Blood Flow and Myocardial Metabolism in Vivo, Proc. Soc. Exper. Biol. & Med. **66**:571, 1947.
5. Holling, H. E., and Zak, G. A.: Cardiac Catheterization in the Diagnosis of Congenital Heart Disease, Brit. Heart J., **12**:153, 1950.
6. Johnson, A. L., Woolin, D. G., and Ross, J. B.: Heart Catheterization in the Investigation of Congenital Heart Disease, Canad. M. A. J., **56**:249, 1947.
7. Zimdahl, W. T.: Disorders of the Cardiovascular System Occurring With Catheterization of the Right Side of the Heart, Am. Heart J. **41**:204, 1951.

FLUORODENSOGRAPHY WITH RADIOPAQUE SUBSTANCE

A New Method for Hemodynamic Investigation

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ELECTROKYMOGRAPHY is a method to study movement in structures that are visible radiologically, and density changes in certain tissues during physiologic activity. It was initiated in 1925 by Chamberlain and Dock[1] in an attempt to register the dynamic changes of the cardiac silhouette. For technical reasons its development was slow until 1945, when Henny and Boone[2] used photosensitive cells endowed with great amplifying power. Their curves had enough amplitude to allow a distinction between the effects due to density and those due to positional changes of the heart. These experiences, together with those of Luisada and associates,[3] Morgan[4] and others have improved the interpretation of electrokymographic curves. In Latin America Dussaillant and associates[5,6] among others, have contributed to the study of this problem.

The most important parts of the electrokymogram are the descending and ascending branches of the ventricular curve. These are due to density changes. We conceived the idea that perhaps the injection of a radiopaque substance would cause such changes in density on arrival of the radiopaque substance in the cardiac cavities or the blood vessel, that they could be better registered on the electrokymogram with the help of adequate photoelectric cells. It seemed to us that the development of such a method would be of great value for the study of many cardiovascular problems.

We decided to test out this hypothesis. In the course of a routine pyelographic study we visualized fluoroscopically, the left ventricle and placed a photosensitive cell close to it. During the injection of 35 per cent Diodrast, we registered an electrokymogram. This curve amply verified our expectation (Fig. 1). The arrival of the radiopaque substance at the left ventricle sensibly altered the curve, whose depth increased as the concentration of Diodrast in the ventricle increased. The analysis of the curve, in relation to the cardiac sounds, shows that the inflections due to positional changes occur during isometric contraction and relaxation, and were not modified in this particular case. But the changes due to density, which occur during ventricular filling and ejection, are very obviously altered.

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Figure 1 shows in three sections the continuous curve registered on that occasion; *A* corresponds to the record before the injection of Diodrast, *B* to the curve during the slow injection of 10 c.c. of Diodrast, *C* to the curve after the injection.

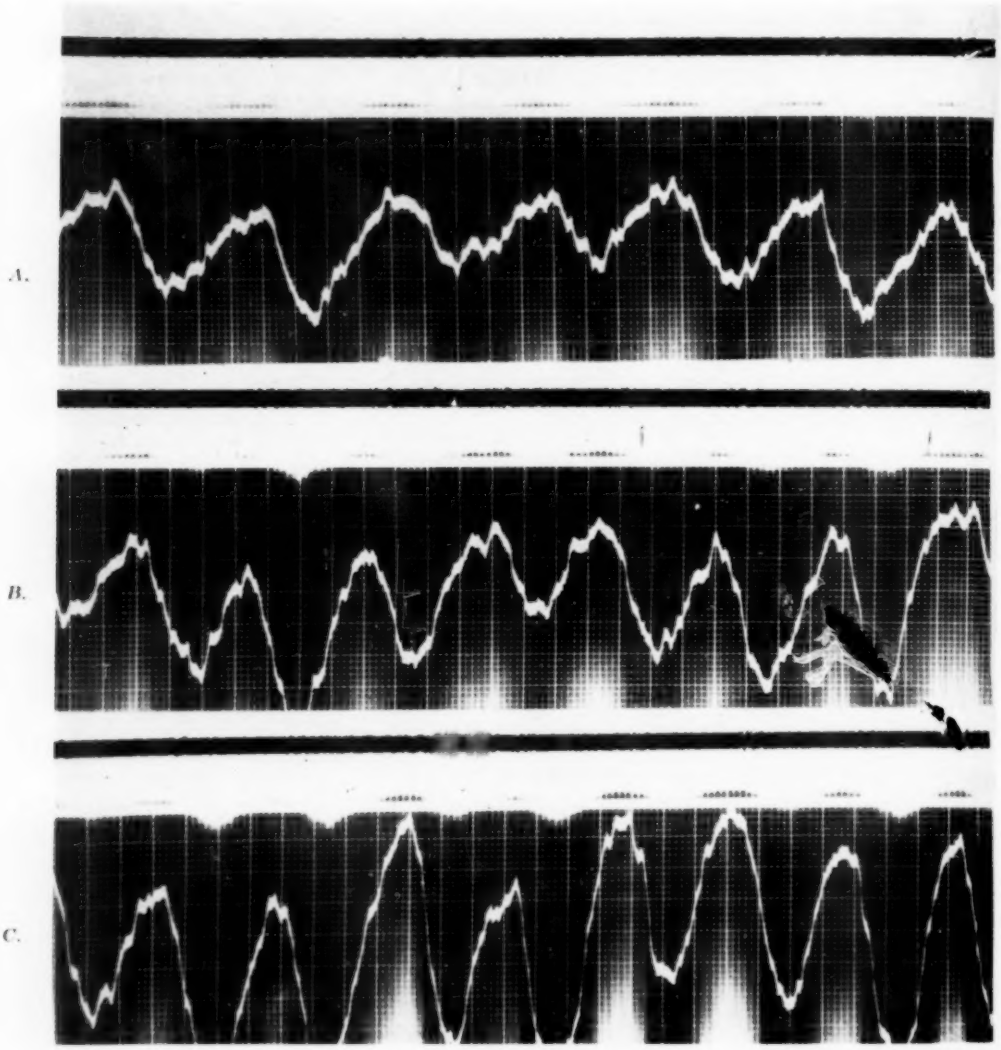

Fig. 1.

A careful review of the literature has not disclosed any previous experiences along these lines. As far as we know this is the first report of fluorodensographic changes produced by the injection of a radiopaque substance.

This new method opens the way to future applications in the field of hemodynamics. We believe that it will be valuable in the study of many problems, among which may be mentioned specifically the following:

I. Measurement of circulation times.
   A. Elbow to left ventricle.
   B. Elbow to right ventricle.
   C. Right ventricle to left ventricle (Pulmonary circulation time).
   D. Other circulation times.

II. Study of circulatory shunts
   A. Diagnosis of some congenital malformations of the heart and blood vessels.
   B. Arteriovenous fistulas.

We first tried to define suitable working conditions, and to standardize the procedure. The following aspects have been considered:

1. Coordination of team work.
2. Standardization of equipment.
3. Selection of the radiopaque substance, its concentration and the quantity of vehicle most suitable to avoid reactions in the patient.
4. Development of standard positions for the patient.
5. A method to register in the electrokymogram the beginning and the end of the injection.
6. Standardization of interpretation of curves.

After careful consideration and study of the above stated aspects, we have reached the following conclusions:

1. The working team should include three persons in charge each of: (a) injecting the substance, (b) placing the photoelectric cell, under fluoroscopic control, close to the left ventricle, and (c) controlling the recording machines (electrocardiograph and electrokymograph).

2. The materials we have used include: (a) Venoclysis outfit, 10 c.c. hypodermic syringe, a 3-way stopcock and a 1 inch 18 gauge needle. (b) Roentgenographic outfit. We have used a vertical 15 Ma. General Electric machine with type B-2 Patterson fluoroscopic screen. (c) Photoelectric cell. We have used an R.C.A. No. 931-A adapted to a Sanborn machine. (d) An electrokymograph, built by Sanborn Co., and rectified to a one-half wave-length. (e) A Steto-Cardiette electrocardiograph built by Sanborn Co.

We feel, however, that a full wave-length apparatus is to be preferred. The reasons for this are well known.

3. As contrast medium we have used 70 per cent Diodrast (Winthrop), 4 c.c. for each injection. This dose has proved adequate and free of any toxic or allergic reactions on patients. It can be used with confidence, with only the general contraindications of iodide compounds.

4. The patient should be placed in a left anterior oblique position when circulation times elbow-right ventricle and elbow-left ventricle are to be determined.

5. The beginning and end of the injection (Diodrast) can be recorded on the curve through the microphone equipment of the phonocardiograph.

6. To interpret the registered curve one measures the time between a point in the middle of the injection and the onset of amplitude changes in the curve.

Our work has been done with only one photo-electric cell. For this reason, in the determination of pulmonary circulation time, we have been forced to measure separately the circulation time elbow-right ventricle and the circulation time elbow-left ventricle and to calculate pulmonary circulation time by subtraction of both. We want to stress, at this time, that the use of a double photoelectric cell will simplify the method, shorten it, and will avoid the necessity of two injections. For the application of this method to congenital heart disease, the double cell will prove practically indispensable.

We have chosen to begin by applying this new method to the determination of circulation times in normal people. This work will be the subject of a separate

communication. To give an idea of the method, we are here reporting one of our curves (Fig. 2.), used to determine the circulation time between elbow and left ventricle. The circulation time in this instance is 6.20 seconds, and the arrow indicates the onset of amplitude changes caused by the arrival of the radiopaque substance in the left ventricle.

A careful study of the curves so far obtained reveals that the modifications in the amplitude of the graphic records is maintained for a certain period of time. This is not identical for different subjects, and the base line of each curve is displaced in some pathologic cases. We believe that in fluorodensography with radiopaque substance not only the onset of changes in the curve is of hemodynamic interest, but that the duration of these changes and the displacement of the base line are likewise of great importance. We believe that these factors may allow analysis of the length of time the radiopaque substance remains in each compartment of the cardiovascular system. This aspect has great possibilities, as it may be the basis for many future applications, among them the study of the functional capacity of the heart, the verification of reflux phenomena, and even perhaps the determination of residual intracavitary volumes.

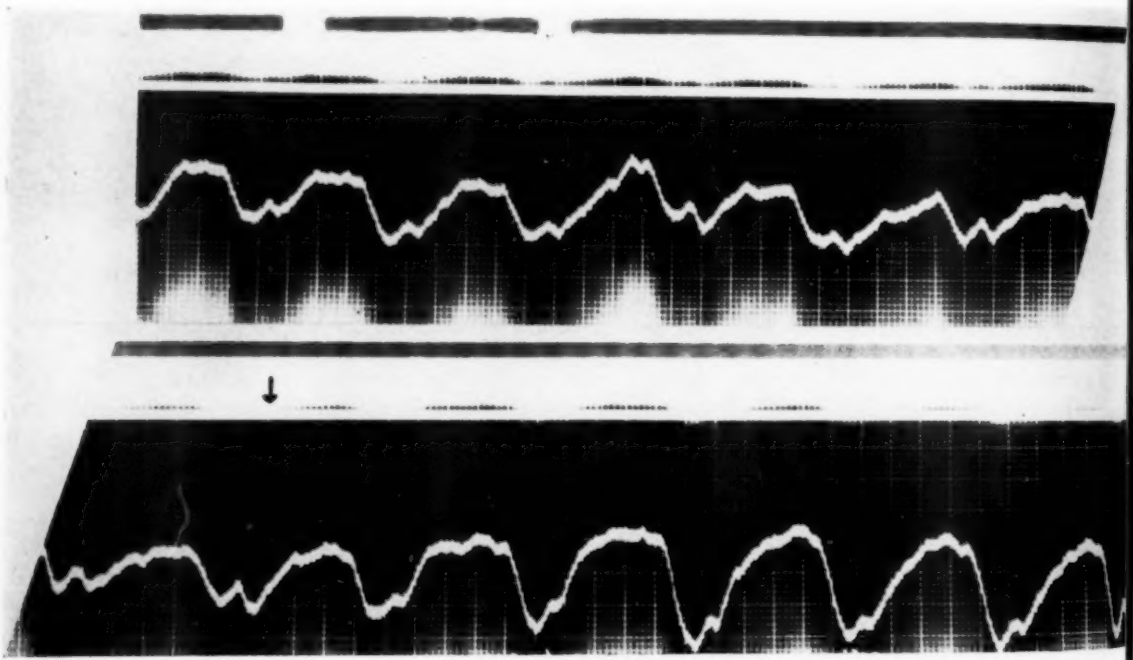

Fig. 2.

SUMMARY AND CONCLUSIONS

Using standard electrokymographic equipment, and on the theory that the main changes in the graphic record of the electrokymogram are due to density effects, the authors have injected intravenously radiopaque material and have shown that the injection produces characteristic changes in the fluorodensogram.

The present paper includes some examples of the curves obtained. Based on these experiences the authors describe a new method for hemodynamic investigation that they call fluorodensography with radiopaque substances.

The procedure used in the application of this method for the determination of some circulation times is described. An analysis is made of the curves obtained in the determination of a circulation time elbow-left ventricle in a normal individual.

The authors believe that this new method opens great possibilities for future developments. Besides its usefulness in measuring circulation times it may prove helpful in the study of arteriovenous shunts, the functional capacity of the heart, residual intracavitary volumes, and other cardiovascular problems. Its use in the determination of pulmonary circulation time is stressed.

The use of double photoelectric cell equipment is advised.

We wish to thank the Instituto Nacional de Cardiologia (México, D.F.) for the use of the facilities that have rendered this research possible; Prof. Narno Dorbecker, chief of the Radiology Department, for his wholehearted encouragement; Prof. Demetrio Sodi Pallares for help in many ways; Dr. Eduardo Fuentes, who first put at our disposal the opportunities needed to verify our theories; and Winthrop Products, Mexico, who generously supplied most of the Diodrast used in this investigation.

REFERENCES

1. Chamberlain, W. E., and Dock, W.: Study of Heart Action With Roentgen Cinematograph, Radiology **7**:185, 1926.
2. Henny, G. C., and Boone, B. R.: Electrokymograph for Recording Heart Motion Utilizing the Roentgenoscope, Am. J. Roentgenol. **54**:217, 229, 1945.
3. Luisada, A. A., Fleischner, F. G., and Rappaport, M. B.: Fluorocardiography (Electrokymography), Am. Heart J. **35**:336, 1948.
4. Morgan, R. H.: Electrokymography, Am. J. M. Sc. **218**:587, 1949.
5. Dussaillant, G., Lepe, A., and Dél Fierro, M.: Electrokimografía. Comunicación Preliminar, Rev. méd. de Chile **77**:5, 307, 1949.
6. Dussaillant, G., Lepe, A., and Gómez, G.: Estudios en Electrokimografía II. Forma y amplitud del electrokimograma ventricular izquierdo normal, Rev. méd. de Chile **79**:4, 237, 1951.

ELECTROCARDIOGRAPHIC MIRROR PATTERN STUDIES. II.

The Statistical and Individual Validity of the Heart Dipole Concept as Applied in Electrocardiographic Analysis

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FROM RELATIVELY early times, the use of the Einthoven triangle, with its underlying assumption of the validity of the dipole hypothesis, to represent the three standard leads in electrocardiography has been accepted as a useful concept, although controversy has continued to the present time regarding the extent of its agreement with facts. Such terms as axis shift and right deviation have become part of the electrocardiographer's language. Acceptance of the triangle and its associated dipole concept as working tools is implicit in any use of a limb-derived central terminal, even in the so-called Unipolar Electrocardiography. The idea of an electrically neutral point derivable externally includes integration of effects from the entire heart at the points of derivation.

More recently, the growing emphasis on spatial analysis of the heart's electric field has made even more desirable and necessary a quantitative study of the dipolicity of the heart not only as concerns the limb leads but also leads in the close neighborhood of the heart, including those affected by electrical components not in the frontal plane. Accordingly the mirror pattern studies which are the subject of the present report were carried out.

As with many biologic investigations, the study of electrocardiographic mirror patterns is essentially a statistical one. Depending on the degree of uniformity among the individual experiments, the quantity of results which is significant statistically may be small or large. The body of data to be presented in this paper is relatively small in comparison with the quantities presented in many careful electrocardiographic studies; the power of the cancellation method is such, however, that the results even from a smaller sample than ours would have been sufficient to establish answers to the most important qualitative questions at hand: (1) is the dipole hypothesis in electrocardiography valid under any circumstances, and (2) if so, under what experimental conditions (that is, electrode placements and central terminal derivations) should it be used? In addition to these, our more detailed data give an answer to the further question

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(3) how good, quantitatively, is the dipole hypothesis when used under the conditions of our experiments (approximately the conditions of conventional electrocardiography)? Finally, we may ask (4) what, if any, are the quantitative effects of variations in the body structure on the electrical measurements thus made? These questions will be taken up in detail after the following discussion of the experimental method used to obtain the answers.

EXPERIMENTAL PROCEDURE AND CANCELLATION METHOD

As indicated in a previous paper,[3] the obtaining and cancellation of a pair of mirror patterns involves the balancing of a threefold bridge. Two of the three variables are eliminated by finding points which are electrically opposite each other across the heart, that is, where mirror patterns exist. These patterns need not be equal in amplitude; they must only be opposite in sign and identical in shape. The third variable is eliminated by combining these two opposite patterns in such a ratio that their weighted sum is zero (cancellation). In practice, the locating of true mirror patterns is by far the more difficult of the two processes.

It is clear, of course, that in order for two electrocardiographic patterns to be mirror patterns, they must look like mirror patterns. The fact that the converse is not true has been the cause of much confusion in electrocardiographic analysis in the past, and of no little difficulty in the present work. It has been found, however, that it is useful to make a rough electrocardiographic map of the chest of each subject prior to the actual search for true mirror patterns. This serves the purpose of indicating the areas where mirror patterns can exist, and thus guides the selection of search location points. Patterns for the map are taken at points on the body determined by a coordinate system. This system was laid out using the intercostal spaces at the sternum as the horizontal levels, labeled in Roman numerals, with the first intercostal space as level I, to level V, and extrapolating to level IX. The circumference of the body at each level is divided into twelve intervals designated by Arabic numerals one through twelve inclusive. The vertical line along the sternum is numbered 1, the left midaxillar line 4, the spinal line 7, and the right midaxillar line 10. Unipolar patterns are taken at all twelve positions on each of the levels I through V, or if time does not permit, at levels I, III, and V. Figure 1 is a mounted set of such mapping patterns arranged according to the coordinates of the patterns.

A glance at this array is sufficient to pick out many pairs of patterns which seem to be very good mirror images. As has been pointed out in a previous paper,[3] however, mere shape is not a sufficient criterion for determination of true mirror patterns. The exact relative timing or phase of each point in a pattern with respect to the phase of the corresponding point in the prospective mirror pattern is critical. If the phases are not identical point-for-point, the two patterns will not cancel, and must therefore not be considered true mirror patterns.

When true mirror patterns are found, it is a simple matter to adjust the cancellation potentiometer to obtain a null. Under these conditions, the fraction of the reference pattern used is just equal in amplitude to the fraction of the search pattern used, so that the two just cancel when added algebraically. If the reference pattern is given too much weight, the cancellation is not perfect, and the cancellation pattern shows the characteristics of the reference pattern. If too little weight is given, the opposite holds true. Figure 2 shows a reference and a search (mirror) pattern, together with ten cancellation patterns obtained with as many settings of the mirror potentiometer dial, as indicated below the patterns. R is the reference pattern taken at coordinates V_5, which indicates the level of the fifth intercostal space at the sternal junction, and about two inches dorsal to the left midaxillar line. The search pattern, S, is located at coordinates III_{12}, which is at the level of the third intercostal space, and about 2 inches to the right of the sternum. As can be seen by examination of the cancellation patterns, the setting of the potentiometer is quite critical with 45 or 46 per cent being the best value. At lower settings the search pattern predominates, and at higher settings, the reference contribution is too large. In general, the best setting of the cancellation potentiometer can be determined to within $\pm$ 2 per cent.

When the search and reference patterns are not true mirror patterns, the best dial setting can still be determined, and usually the cancellation pattern is small and diphasic or triphasic. When

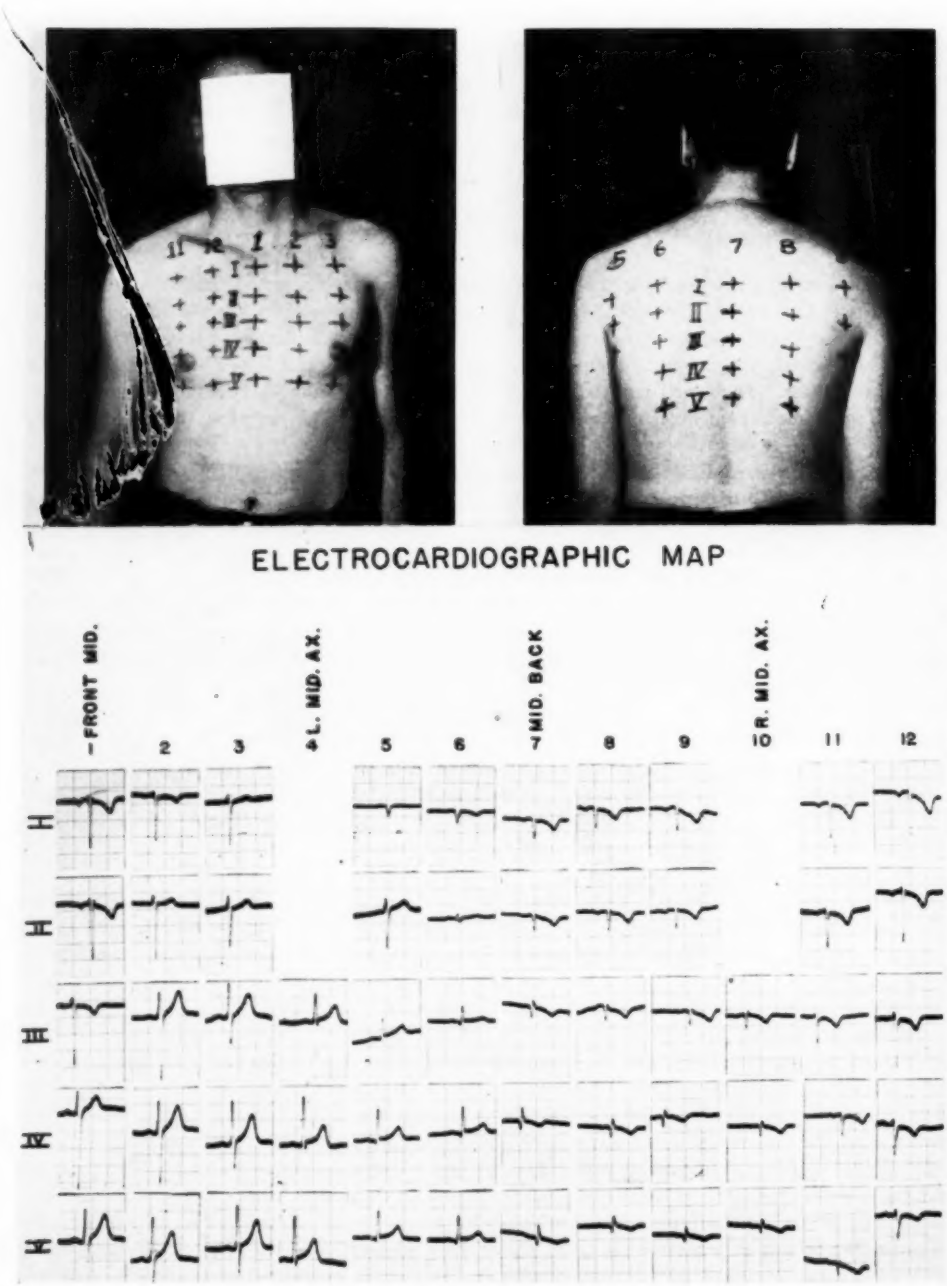

Fig. 1.—V leads are taken at 56 locations on the torso and arranged to form an *electrocardiographic map*. Roman numerals designate horizontal lines around the body and refer to intercostal space levels at the sternum. Arabic numerals designate vertical lines, *1* being the midsternal line, *4* the left midaxillar, *7* the midback, and *10* the right midaxillar line. Other lines are spaced evenly between these reference lines. Examination of this map reveals many pairs of apparently good mirror patterns at points approximately opposite each other across the heart.

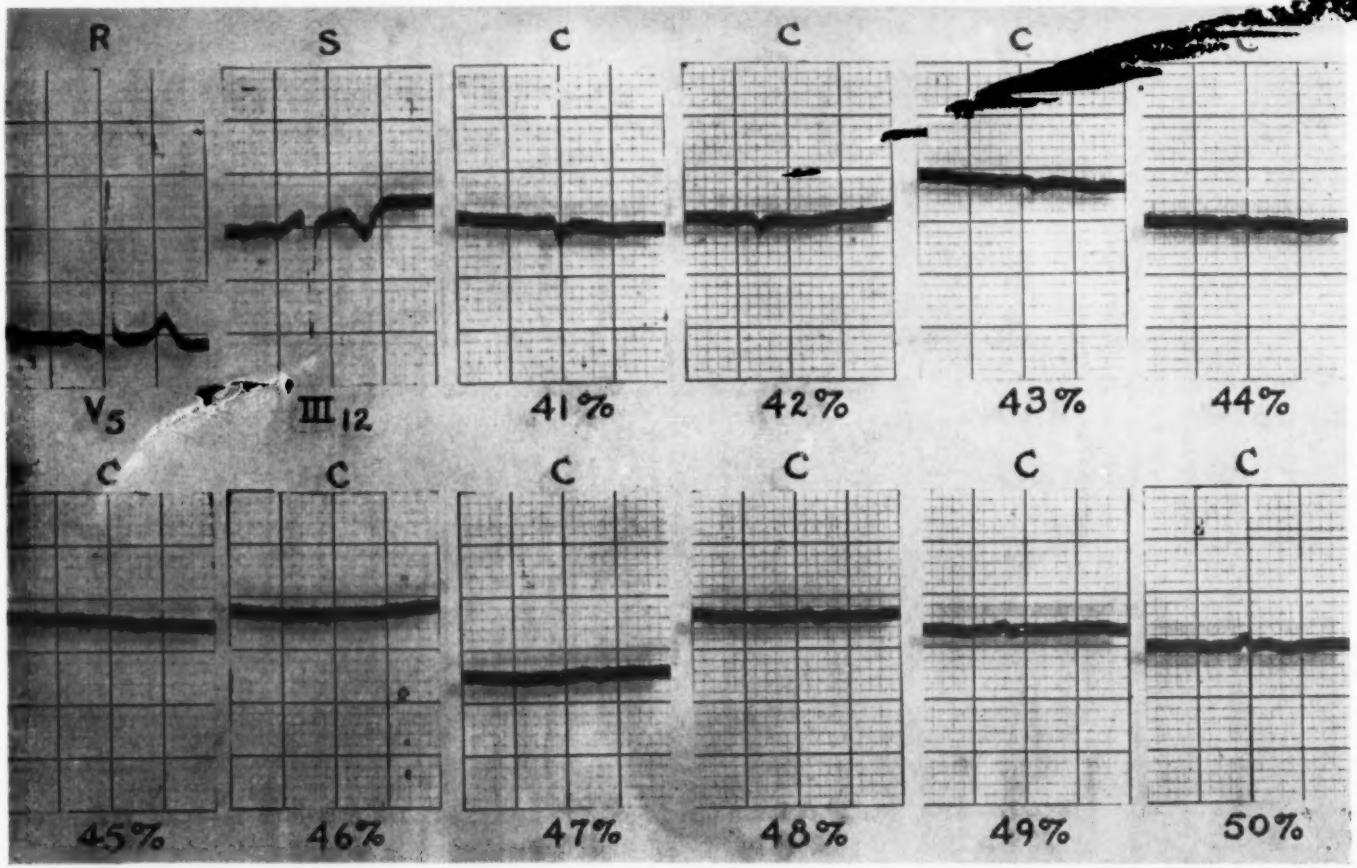

Fig. 2.—Effect of mirror potentiometer setting on cancellation excellence. *R* designates the reference pattern and *S* the search pattern in this mirror pair. The cancellation pattern is taken for each of ten settings of the mirror potentiometer dial, with 45 per cent or 46 per cent the best setting. When the dial reading is lower, the search pattern predominates in the cancellation result; when the dial reading is higher, the reference pattern predominates.

the best cancellation obtainable with any particular pair of search and reference locations (initially determined by reference to the electrocardiographic map) is not a good null, a better search location is sought. This continues until a satisfactory cancellation is obtained, or until it is decided that such a cancellation does not exist or cannot be found in the time available. In Fig. 3 are shown two reference patterns, and three search patterns for each, together with the best cancellations available for the combinations. For the reference location V_4 (fifth level at the left midaxillar line) search location III_{11} does not produce a true cancellation pattern, although qualitatively the pattern looks like a mirror image of the reference pattern. Examination of the cancellation patterns shows, however, that the phase of the reference pattern leads that of the search pattern by a measurable amount. The search pattern at position II_{11}, about one and one-half inches above the previous pattern is nearly in phase with the reference pattern. The P and T waves do not cancel perfectly. With the search electrode on the right arm, which corresponds roughly to location I_{10} in the coordinates used, the phase of the search pattern has reversed with

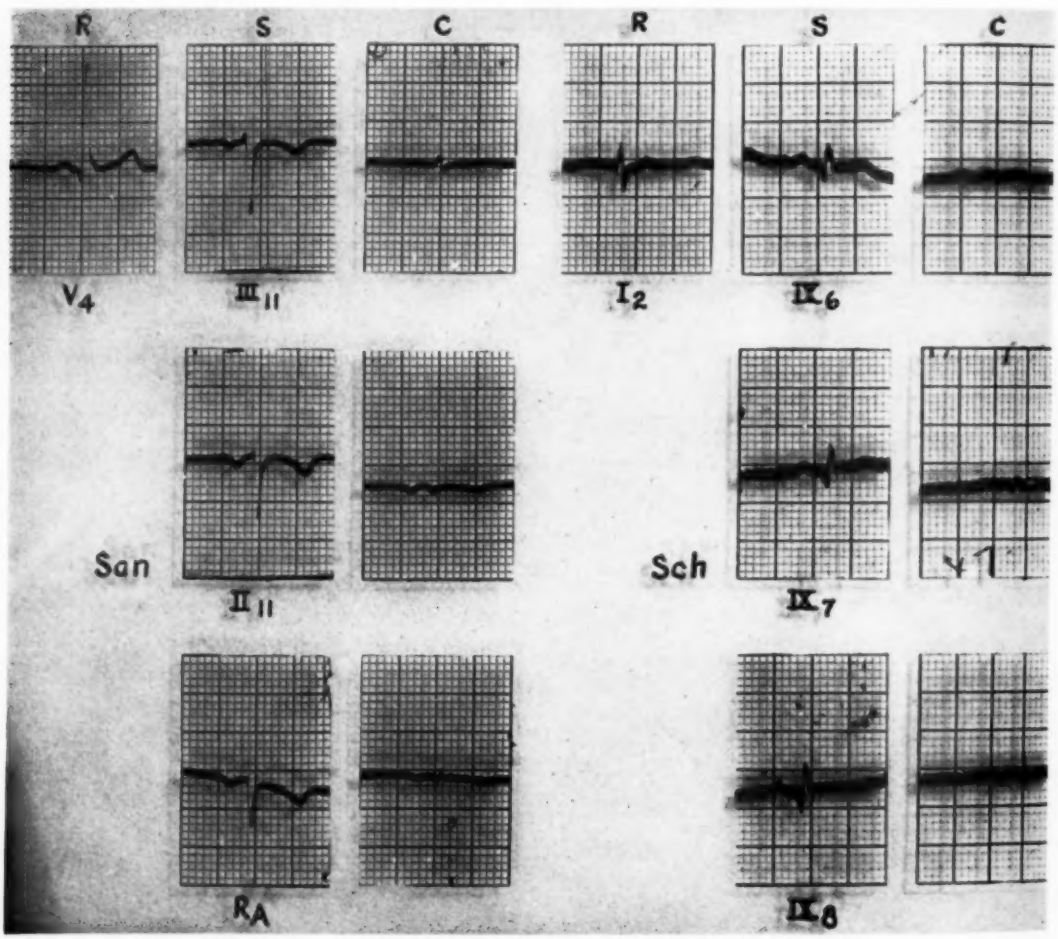

Fig. 3.—Effect of search electrode location on cancellation excellence. Two reference patterns are shown in this figure; for each reference pattern, three search patterns and their corresponding best cancellation patterns are shown. In each case, the three search patterns appear equally valid as mirror images of the reference pattern. However, one of the three is actually better than the other two in each case. See text for explanation of location numbers.

respect to that of the reference pattern, and now leads, rather than lags, the reference. In the other case in Fig. 3, location IX_6 is the best search location for the reference at I_2. Locations IX_7 and IX_8 are successively farther away from the mirror location. In general, search locations separated by as little as one inch show definite differences in cancellation quality. In the limited time available for study of any one subject, it is generally not feasible to locate the very best search position.

In brief, then, the experimental procedure calls for the following steps: a reference location is chosen; a spot which appears anatomically and according to the electrocardiographic map of the subject to be a likely position for a mirror pattern is chosen for the search electrode; the best possible cancellation is made by adjustment of the balance potentiometer; an improvement is attempted by moving the search electrode in a direction indicated by the map and by experience, and the best cancellation again determined; this continues until a satisfactory cancellation is obtained, or until it appears impossible to find one. This process is repeated for another reference location, and so on until mirror patterns have been found at several locations distributed about the heart. These locations are recorded in tabular form, and by means of the special photographic technique described in a preceding paper.[3] Table I shows a typical set of data obtained during a two-hour experiment on a patient.

TABLE I. MIRROR PATTERN DATA ON A TYPICAL SUBJECT*

REFERENCE LOCATION	TRIAL NUMBER	SEARCH LOCATION	MIRROR-POTENTIOMETER READING (%)	CANCELLATION
V_4	1	RA	34	Fair (best)
	2	II_{11}	26	Poor
IX_2	1	II_6		NG
	2	$-I_7$	30	Poor (best)
	3	$-I_8$		NG
III_{11}	1	LA	36	Poor
	2	IV_6	26	Poor
	3	IV_5	23	Fair
	4	III_5	34	Exc. (best)
III_3	1	V_7	46	Exc. (best)
V_5	1	II_{11}	59	Exc. (best)

*Subject # 50. E. L. H. (Posterior Infarct)
NG = no good.

As can be seen from a glance at the data in Table I, it is occasionally possible to find an excellent cancellation on the first attempt. More often, it takes several trials, and even then, the cancellation may be only fair or poor. With experience, one learns to judge fairly well whether further attempts will result in finding a significantly better mirror location within reasonable time limits. The excellence of cancellation for any given location is, of course, calculated on the basis of the best cancellation found.

In the analysis of the data obtained for each pair of mirror patterns, the cancellation coefficient defined in a previous paper[3] is used as an indication of the excellence of cancellation. Since this coefficient is equal to the residual fraction of the search and reference voltages which cannot be cancelled by this technique, the value of the coefficient must lie in the range from zero (perfect cancellation) to one (no cancellation). This range is divided arbitrarily into sections

which are labeled excellent, good, fair, bad, on the basis of experience with the average distribution found experimentally. The range of cancellation coefficients is therefore divided as follows:

cancellation coefficient less than 0.08 excellent
less than 0.12 good
less than 0.16 fair
less than 0.20 poor
less than 0.40 bad
greater than about 0.40 no cancellation
(cancellation coefficient greater than 0.6 has never been found)

A coefficient of this type may be defined for each complex or wave of the electrocardiogram. On the basis of the spatial vector pattern for the electrocardiogram, the peak-to-peak amplitude of any complex measures the projection of that complex in the direction determined by the search and reference electrode placement. It is not, therefore, worth while to analyze the Q, the R, and the S parts of any QRS complex separately. In practice, the P amplitude has proved too small for useful analysis. The T wave can be examined very well in most cases and often cancels somewhat differently from the QRS complex.

RESULTS

A. *Distribution of Cancellation Coefficient.*—Mirror pattern cancellations have been obtained on seventeen normal subjects and thirty-seven cardiac patients. Because the procedure is a lengthy one, consuming from one and one-half to three hours, and because the endurance of patients is generally less than that of normals, only three-fifths as many cancellations were obtained from each patient, on the average, as from each normal subject. For purposes of analysis, the total numbers of excellent, good, fair, poor, and bad cancellations were found for each type of subject, and the percentage of distribution calculated. The average cancellation coefficient was also found for each group. Table II*A* is a summary of these data.

TABLE II*A*. SUMMARY OF CANCELLATION COEFFICIENT VALUES USING WILSON CENTRAL TERMINAL

GROUP	NUMBER OF SUBJECTS	NUMBER OF CANCEL-LATIONS	NUMBER OF NO-CANCEL-LATIONS	% OF QRS CANCELLATIONS					AV. CANC. COEFF.
				EXC.	GOOD	FAIR	POOR	BAD	
Patients	37	142	19	25	13	12	16	34	0.16
Normals	17	106	4	40	22	14	12	12	0.11
All Subj.	54	248	23	31	16	13	15	25	0.14

The table shows that the distribution of the QRS cancellation coefficient is different for normals and patients, with the patients generally having more cancellations in the poorer categories. Mirror patterns in patients will be discussed in detail in a forthcoming paper. It should be pointed out that the over-all averages are for 110 cancellation attempts in normals and 161 in patients. This is not the distribution in any random sample of the population at large, so that over-all figures for the total population should probably be taken as substantially

the figures for our normal sample alone. Thus we may say that some 60 per cent of the cancellation coefficients are in the excellent and good categories with only about 12 per cent in the bad class.

As has already been mentioned, the above data are for QRS complex cancellations. The P waves were too small in amplitude to make any cancellation attempt useful. The T wave was also cancellable, but not necessarily in exactly the same location or at the same mirror potentiometer setting as the QRS complex. The study, therefore, concentrated on the mirror characteristics of the QRS complex.

Perhaps a clearer picture of the distribution of the normal cancellation coefficient is given by the graph of Fig. 4*B*. The values are concentrated in the range from zero to 0.20, and are nearly uniformly distributed in the range from zero to 0.10. It should be pointed out that with a distribution such as this, it would not be meaningful to specify an average deviation from the mean or a standard deviation for an individual cancellation coefficient, since the distribution does not resemble a normal curve.

On the other hand, if these data are examined on the basis of the average cancellation coefficient for an individual subject, the curve of Fig. 4*A* is obtained. From this it is seen that although a substantial fraction (about 5½ per cent) of all cancellation coefficients are perfect (in the range from 0.00 to less than 0.01), no subject had a perfect average for all his cancellation coefficients. Indeed, the distribution of such averages looks something like a normal curve, and this is also true of patients. When compiled in this manner, our figures are those of Table II*B*. The error shown is the average deviation from the mean.

TABLE II*B*. SUMMARY OF SUBJECT-AVERAGE CANCELLATION COEFFICIENTS USING WILSON CENTRAL TERMINAL

GROUP	NUMBER OF SUBJECTS	% OF SUBJECTS WHOSE AV. QRS C. C. IS:					AV. CANC. COEFF.
		EXCELLENT	GOOD	FAIR	POOR	BAD	
Patients	37	19	16	13	30	22	0.15 ± .06
Normals	17	18	35	41	6	0	0.11 ± .03

In order for any such figures as those in Tables II*A* and *B* concerning the distribution of the cancellation coefficient to be valid, the magnitude of the coefficient should be independent of all factors except the dipolicity of the heart. Ideally, there would be no areas on the torso where local patterns would replace dipole patterns, and of course, the cancellation excellence would be independent of the amplitudes of the electrocardiograms which are opposed to obtain the null. The first of these points will be taken up more fully in the following section of this paper (Results B). To check the second point, a plot was made of the value of the cancellation coefficient as a function of the amplitude of the reference and search patterns involved. The graph of Fig. 5 which results, fails to show any interdependence of these two variables with the possible exception of the cancellations

obtained from very small reference and search amplitudes (the sum of the amplitudes of the two patterns being less than 10 mm.). This important result shows that the dipolicity of the patterns on the surface of the body is not a function of their electrical distance from the heart.

It has been pointed out that the operation of determining accurate mirror locations is the more critical one in getting good cancellations. It has also been indicated that the best mirror location is seldom found for any given reference location; that is, by further search it is usually possible to improve the cancellation by moving the search electrode to a new location a short distance from the one

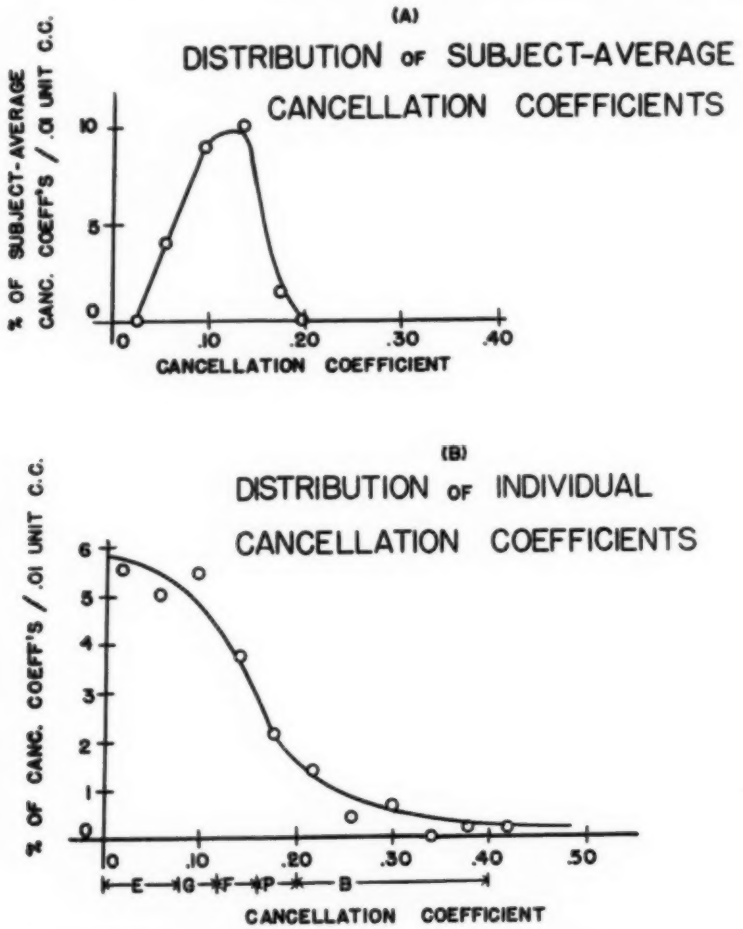

Fig. 4.—Distribution of cancellation coefficients in normal subjects. *A*. All the cancellation coefficients obtained on each subject are averaged and the frequency of occurrence of each value of this average plotted as a distribution curve. For example, a point at ordinate 9 and abscissa 0.10 implies that 9 per cent of the average cancellation values will lie between 0.095 and 0.105. Because of the limited amount of data available, blocks of coefficient 0.04 units wide are used in constructing the graph and normalized to an 0.01 basis. *B*. In this curve all the cancellation measurements made on normal subjects are lumped and plotted as a distribution curve on the same basis as *A*. Comparison of the two curves shows that cancellation excellence does not tend to be characteristic of an individual. The letters below the abscissa refer to cancellation ranges from excellent through good, fair, poor, and bad to the range classed as no-cancellation. The curve does not quite reach the axis in the figure because an occasional very bad cancellation in the range 0.4 to 0.6 is found.

chosen after the necessarily limited time allotted to each mirror pair. This may be illustrated by referring again to Fig. 3. For the reference pattern at V_4, the best cancellation coefficient obtainable at search location III_{11} was 0.17. At RA, the best was 0.10, and at II_{11} it was 0.06. In the case of reference location I_2, the best cancellation coefficients obtainable at search locations IX_6, IX_7, and IX_8 were respectively 0.16, 0.12 and 0.09. By extrapolation from a few cases where an exhaustive search was made to locate the actual best obtainable cancellation coefficient, it is possible to establish that the best cancellation in any given case is on the average about 20 per cent better than that actually obtained in the restricted time. The extrapolation factor is, therefore, taken to be about one-fifth of the value of the coefficient obtained. That is, 0.02 in 0.10, and so forth.

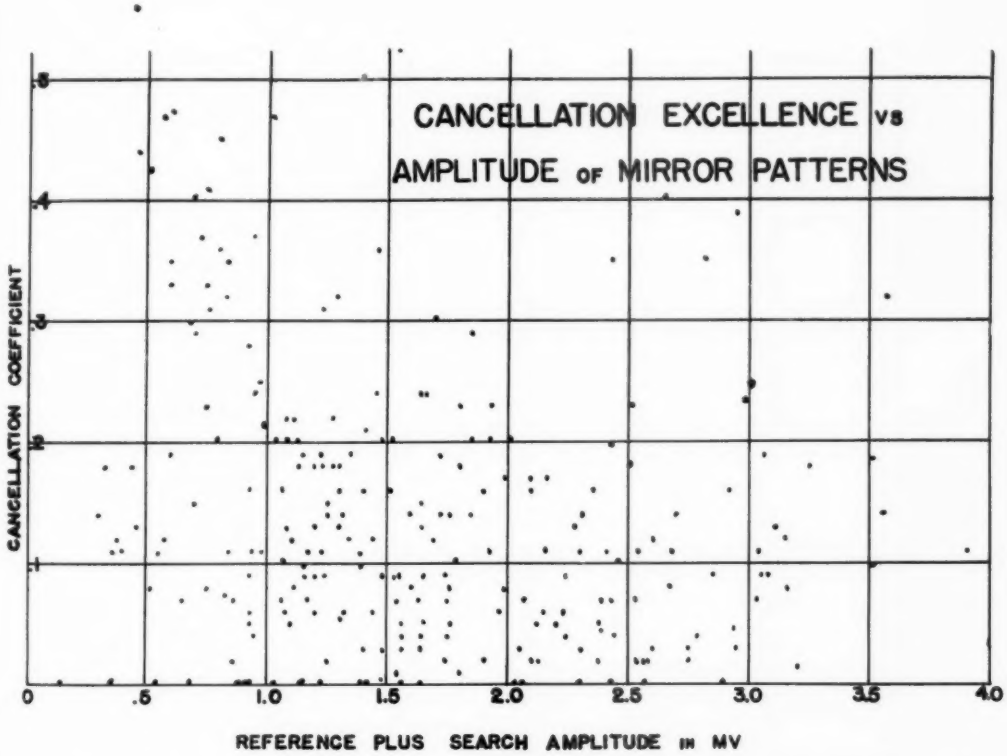

Fig. 5.—Effect of search and reference pattern amplitudes on cancellation excellence. For each pair of mirror patterns found, the cancellation coefficient is plotted against the sum of the amplitudes of search and reference patterns. The resulting scatter diagram shows no significant correlation between these two variables. The excellence of cancellation of a given pair of mirror patterns is therefore taken to be independent of the amplitudes of the patterns involved.

In this connection it should be said that the cancellation of the T wave can almost always be improved in the same way, that is, by relocation of the search electrode. The fact that the best cancellation of the T wave does not necessarily occur at the same location as the best QRS location is taken to mean that the heart's electrical center has undergone a translation between the QRS and the T

phases. However it has been found as feasible to cancel the T wave as the QRS complex although the relatively lower amplitude of the former makes it more difficult to obtain precision in calculating the magnitude of the coefficient.

After the application of the extrapolation factor indicated above, the results of the cancellation coefficient studies may be summarized as follows:

TABLE III. CANCELLATION COEFFICIENTS FOR VARIOUS SUBJECTS

GROUP	NUMBER OF SUBJECTS	NUMBER OF CANCELLATIONS OBTAINED	NUMBER OF CANCELLATIONS PER SUBJECT	EXTRAPOLATED AVERAGE CANCELLATION COEFFICIENT
Patients	37	142	3.8	0.13+
Normals	17	106	6.2	0.09+
All Subjects	54	248	4.6	0.11+

Again it should be noted that in obtaining the average of the cancellation coefficients for all subjects, the weighting as between normals and patients is abnormal, and the extrapolation to the population as a whole should probably be done on the basis of the normal sample only, thus giving a value of 0.09 for the average cancellation coefficient. This means that on the average all but 9 per cent of the potentials appearing at appropriately chosen locations opposite each other across the heart may be described on the basis of a single dipole-like source at some electrical center of the heart.

We are now in a position to answer the first and third questions opening this paper, as well as a substantial portion of the second question. It seems clear that under most circumstances, the dipole hypothesis is valid. A substantial number of perfect cancellations (cancellation coefficient less than 0.01) has been found, and these are distributed in several directions about the heart. It is so unlikely as to be out of the question that independent projection areas such as those postulated in Unipolar Electrocardiography should be so perfectly synchronized as to present perfect mirror patterns on all sides of the heart. As to how good the concept is, quantitatively, we have already seen in the previous paragraph that on the average approximately 90 per cent of the potentials appearing at the surface of the body may be ascribed to a dipolelike source. This is sufficiently good for use in most semiquantitative analyses, including stereovector electrocardiography. And finally, these conclusions are based on the use of the Wilson central terminal as reference for the mirror patterns, indicating that this terminal is really quite a satisfactory neutral reference.

B. *Mirror Pattern Locations.*—It was mentioned earlier that although patterns which seem to be good mirror patterns may actually be false, those which do not seem to be good ones can never cancel satisfactorily. The hypothesis of the existence of mirror patterns (based on a study of electrocardiographic maps) is not new.[1,2] Such studies enable us to say that within wide limits, mirror patterns appear only at points at least approximately anatomically opposite each other across the heart. This conclusion is reinforced by the more powerful cancellation

technique. Figure 6 is a sketch showing two typical mirror location pairs. The small circles are reference locations, and the larger, diffuse areas, the corresponding search locations at which mirrors were found in various individuals. These mirror locations were obtained by including the results of all the cases in which the corresponding reference location was used, and where a cancellation coefficient of 0.20 or less resulted. The size of the mirror area indicates the range of locations of mirrors found for the given reference location, and may be specified by the notation ± I and ± 1 for each location. That is to say, the average deviation from the mean mirror location is only one unit of the coordinate system in any direction; the mirror pattern is thus usually found within a circle of about 2-inch radius from this location.

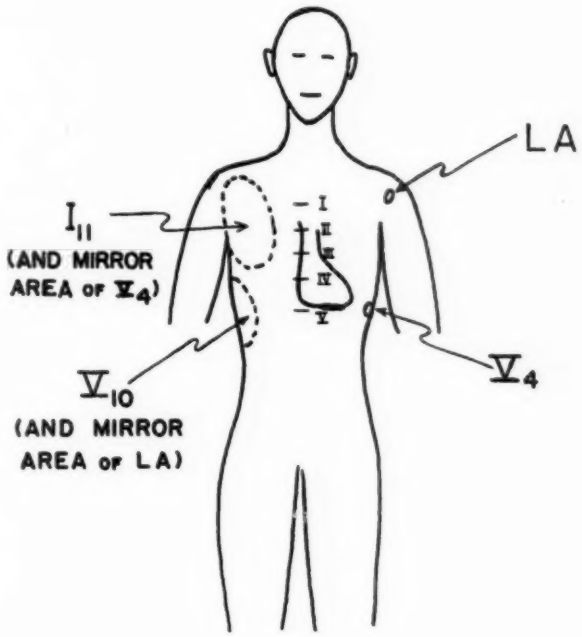

Fig. 6.—Location of mirror patterns. The location of the search electrode which will give a good mirror pattern for the pattern from a given reference electrode location differs from person to person, but remains within a fairly small area surrounding an average value. The figure shows two reference locations and the corresponding mirror search location areas.

Mirror patterns were obtained at nearly 100 points in the coordinate system during the course of the program in which fifty-four subjects participated. In Table IV are listed the thirty-five coordinate locations at which at least four cancellations were obtained where $C \leq 0.20$. In the second column are the average cancellation locations. These may be compared in the third column with the anatomical mirror locations—those places anatomically opposite the reference location across the heart. Columns 4, 5, and 6 list the numbers of cancellations in the poor or better, the bad, and the no cancellation classes, and column 7 lists

TABLE IV. LOCATION OF MIRROR PATTERNS

REFERENCE LOCATION	AV. MIRROR LOCATION (THOSE ≤ 0.20)	ANATOMICAL MIRROR LOCATION	NO. OF CANC. WHICH ARE ≤ 0.20	NO. OF CANC. WHICH ARE > 0.20	NO. OF NO CANC.	QRS CANC. COEFF.
Head	LL	LL	4	1	—	0.11
I_1	LL	LL	5	0	2	0.11+
I_2	VII_6	LL	14	4	—	0.15
I_3	VI_7	IX_7	5	1	1	0.17+
LA	V_{10}	IX_{11}	11	1	—	0.10
RA	V_4	V_4	31	2	—	0.09
I_{11}	VI_4	VII_4	9	1	—	0.10
II_2	VI_7	VII_6	4	2	—	0.20
II_{11}	V_4	VII_4	14	2	—	0.09
III_8	V_2	IV_2	6	1	—	0.15
III_{10}	V_3	V_3	4	0	—	0.13
III_{11}	V_5	IV_4	5	1	—	0.06
IV_2	IV_8	IV_7	8	1	1	0.09+
IV_3	III_8	IV_9	4	0	—	0.10
IV_6	V_1	IV_1	7	2	—	0.16
IV_7	IV_3	IV_2	7	2	—	0.09
IV_8	V_2	IV_2	5	0	—	0.10
IV_{10}	V_4	IV_4	4	0	—	0.08
IV_{12}	V_6	IV_5	7	2	—	0.17
V_1	IV_5	IV_6	6	2	4	0.16+
V_2	IV_8	III_8	20	1	4	0.12+
V_3	II_9	III_9	7	2	2	0.15+
V_4	I_{11}	III_{11}	47	2	2	0.09+
V_5	III_{12}	III_{12}	9	2	—	0.11
V_6	III_2	IV_1	11	2	—	0.14
V_7	III_2	IV_2	7	3	—	0.18
V_8	IV_2	IV_2	4	1	—	0.17
V_{10}	III_4	IV_4	5	0	—	0.09
VI_2	II_9	I_7	4	1	1	0.11+
VI_3	II_{10}	I_9	5	2	—	0.10
VI_4	II_{10}	II_{10}	9	0	—	0.08
VII_4	0_8	0_{10}	4	0	—	0.07
IX_3	$-I_7$	$-II_9$	6	6	—	0.20
IX_{11}	I_5	$-II_5$	5	2	—	0.18
LL	0	Head	13	3	—	0.14

the value of the average cancellation coefficient (not extrapolated) for the given reference location, using all the values obtained, including the bad cancellations.

This table reveals two important points. First, although mirror axes are not necessarily straight lines, neither do they deviate greatly from straight lines. Second, the cancellation coefficient is not a function of local or remote leads. The first point is important because even though the surface of the body deviates markedly from the spherical or cylindrical shape favored by mathematicians, and therefore is expected to cause corresponding deviations in the paths of the electric currents, the distortions caused by the body shape and the internal inhomogeneities are much smaller than might have been expected.

The second point is important in its application to the study of the dipole hypothesis. The heart may apparently be treated as a dipole even in the case of precordial electrodes with about as much justification as in the case of the more distant leads.

The first point is illustrated in Fig. 2 of the preceding paper.[3] The lines joining reference and search locations are evidently not the actual, or electrical, mirror axes. Yet they do all meet in a rather limited volume. A composite picture summarizing these data is presented in Fig. 7. A rough three-dimensional graph was made, consisting of a cylindrical form of approximately elliptical cross section to simulate an average torso, with coordinates marked off on it similar to those used in the mapping procedure. Wires were run from each location for which one or more mirror patterns were found, to the average location of the mirror patterns. With the wires all in place, bioplastic was poured in and hardened, so that a transparent cylinder was obtained. The wires are seen to meet in a diffuse region approximately corresponding to the location and size of the heart.

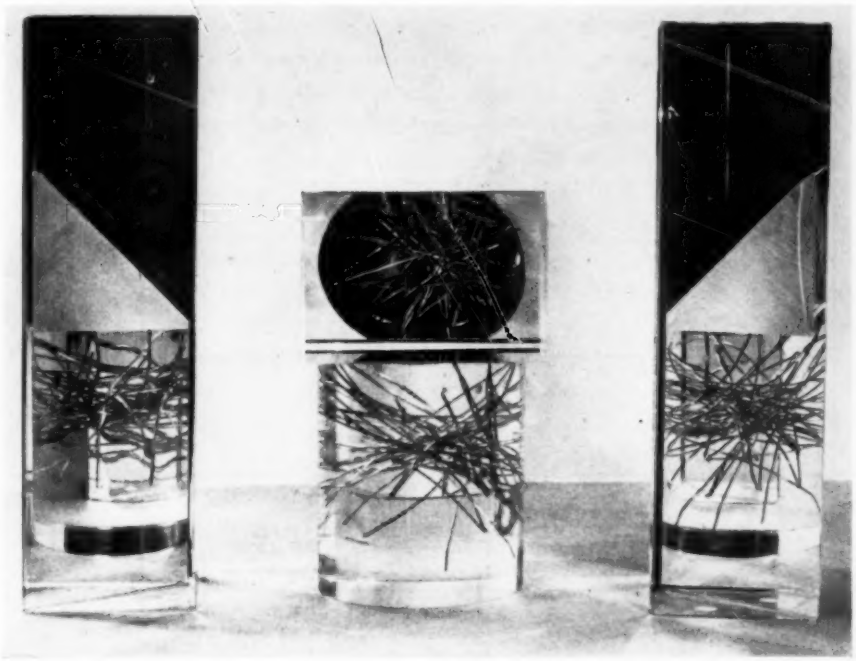

Fig. 7.—Average locations of mirror patterns. A scale model was constructed using a wire to represent each average mirror axis for all subjects studied. Each wire runs from a given reference location to the corresponding average mirror search location. The wires were arranged in a hollow cylindrical model of an average torso, and the model then filled with bioplastic material, to make a solid transparent model. Three prisms placed around the model provide a top view and two side views in addition to the direct front view.

In order to determine whether the excellence of cancellation was a function of location on the body, the graph of Fig. 8 was made. The axes represent the coordinate system previously described for locating points on the torso, with levels I through V at the intercostal spaces along the sternum, and levels VI through IX and levels O and −I extrapolations below and above. H represents the head, and L the level at which the legs join the trunk and hence the legs themselves. L_3 is thus the coordinate pair assigned to the left leg; L_{11} would be that for the right leg. On this graph, a dot is placed to indicate the location of

each excellent and good cancellation (cancellation coefficient 0.10 or less). A cross is used to indicate each bad cancellation (cancellation coefficient 0.21 or greater). Both distributions are relatively uniform, indicating again that the excellence of cancellation is not a function of the body coordinates at which patterns are taken.

The above data have given us the remainder of the answer to our second question: under what experimental conditions is the dipole hypothesis usable? The heart apparently gives dipole-like patterns, when referred to the Wilson central terminal, at all positions on the body. To approximately the same extent, precordial leads and remote leads represent one-dimensional projections of a central vector. On the average, about 10 per cent of the total pattern in any location can be ascribed to effects other than a simple integration of the heart's

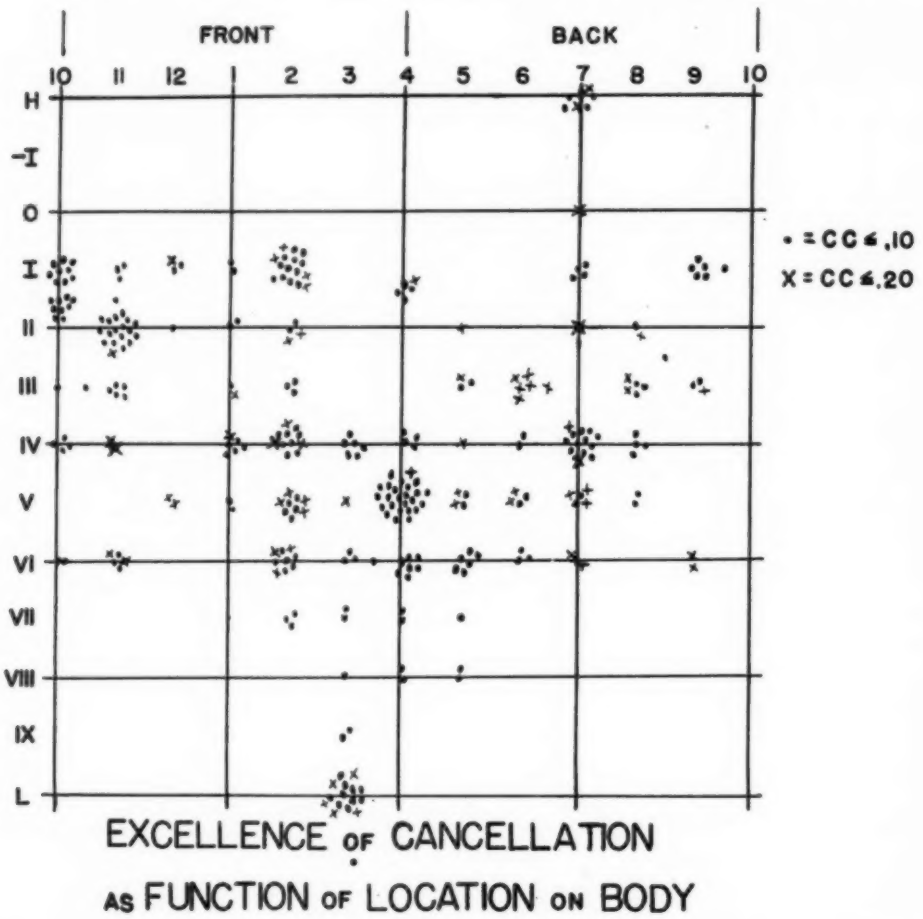

Fig. 8.—Distribution on the body of good and bad cancellations. The coordinates shown are the same as those of the electrocardiographic map of Fig. 1. Levels *O* and *−I* are extrapolations up from level *I*, with *H* indicating head. Levels *VI* through *IX* are extrapolations down from level *V*, with *L* indicating leg locations. Each cancellation with a coefficient of 0.10 or less is indicated on this map by a dot, and each with a coefficient of 0.20 or more is indicated by a cross. No significant correlation between location and cancellation is apparent in this scatter diagram.

entire electrical activity in the form of an equivalent dipole. These results are of direct importance in evaluating any proposed scheme of electrocardiographic interpretation.

C. *Effect of Body Structure on Electrical Measurements.*—The behavior of a dipole in an infinite conducting medium may be handled conveniently by reasonably simple mathematics. Extrapolation from this ideal case to the bounded conditions met with in human electrocardiography is certainly not feasible on the quantitative level, but it is not too much to hope that at least some qualitative relations might be deduced. For instance, in the ideal case, the potential at any distance from the dipole is an inverse function of the distance squared. From this it should surely be safe to infer that in the body, the electrocardiographic amplitude should decrease with distance from the heart. This in turn should affect the third bridge-balancing operation. The mirror potentiometer setting depends on the relative electrical distances of the reference and search locations from the heart, and these in turn should depend on the physical distances, though what the exact relationship should be is not readily predictable.

Even in the ideal case the inverse square law breaks down at distances which are not large compared to the size of the dipole. That is to say, the dipole looks like two discreet sources of current from points nearby, and the predictions from dipole theory, which are based on large comparative distances, fail to hold at the small distances. Extrapolating, therefore, we should expect to find less good dipolicity in subjects whose hearts are larger in comparison to their chest dimensions than we would find in normal persons.

Studies were made of these two points with the aid of chest and heart roentgenogram measurements,* in which both the position and the size of the heart relative to the chest were computed. The first point was checked by plotting the ratio of reference to search pattern amplitude along a right-left mirror axis ($V_4 - I_{11}$) against the ratio of the right and left anatomic distances of the heart center from the sides of the body. This graph is shown in Fig. 9*A*. No significant correlation is visible between the two factors.

The second point was investigated by plotting the cancellation coefficient obtained on a right-left mirror axis ($V_4 - I_{11}$) against the ratio of the right-to-left diameters of chest and heart. This plot, shown in Fig. 9*B*, fails to reveal any clear-cut relationship.

This enables us to answer the fourth question asked at the beginning of this paper. Evidently, linear distances inside the body are not translatable into electrical distances in any simple manner, nor do the relative diameters of chest and heart, in the ranges encountered, affect strongly the dipolicity of the current distribution. It is true, however, that the factor of electrical distance inside the body does exist, since there is a marked effect of mirror location on the setting of the cancellation potentiometer needed to balance the bridge. What these studies show is merely that there is no obvious way of predicting the magnitudes of these electrical distances from the body dimensions.

*We are indebted to Dr. James Dahl of the Department of Physiological Hygiene, University of Minnesota, for his assistance in obtaining and evaluating these measurements.

DISCUSSION

The technique of mirror pattern cancellations is a very powerful method for the study of the dipole theory. Only under very special and unlikely circumstances of orientation and synchronization could a current source such as the heart produce even one pair of mirror patterns, perfect both in phase and amplitude,

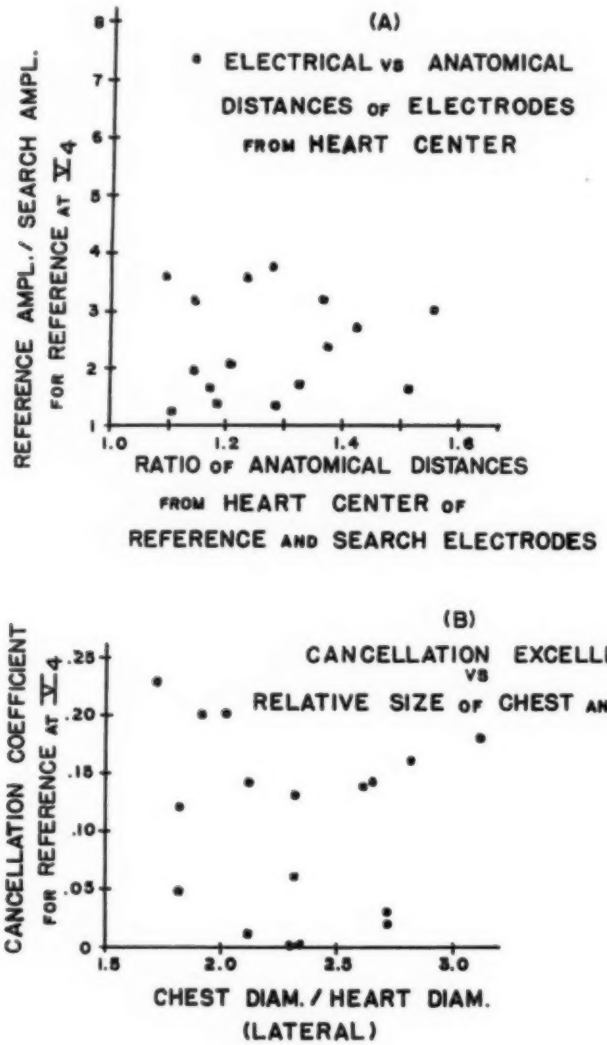

Fig. 9.—Relations between body dimensions and body electrical characteristics. *A* shows a comparison of electrical and physical distances from the heart center. The abscissa represents the ratio between the physical distances (from roentgenogram measurements) to reference and search electrodes on a lateral axis through the heart, and the ordinate represents the ratio between the reference and search pattern amplitudes, which may be taken as a measure of the electrical distances involved. No correlation is apparent. *B* shows a comparison of cancellation excellence and the relative size of the heart. The abscissa represents the ratio between the chest and heart lateral diameters, and the ordinate represents the cancellation coefficient for a mirror pair on a lateral axis. The lack of correlation here indicates that even relatively large hearts act as much like dipole sources as do smaller hearts.

if it were not behaving as a dipole. That is to say, it would be extremely improbable that two local patterns, originating in different parts of the myocardium would be synchronized so perfectly, and agree so strikingly in wave form, as to be cancellable by the technique used. The probability of a nondipole source producing several such pairs of local patterns in widely differing orientations becomes vanishingly small. Conversely the existence of even a single subject on whom it is possible to find pairs of mirror patterns in several directions, all cancelling excellently, gives powerful support to the dipole hypothesis. A striking example of such a phenomenon was subject number 5 for whom the average coefficient for fifteen cancellations at widely distributed locations on the body was only 0.037. In such a subject it seems clear that the three conditions necessary for the general formation of mirror patterns were amply fulfilled. That is, his heart's electrical activity could be represented as a single electric vector, his body acted as an essentially distortion-free conducting medium, and the Wilson central terminal was nearly ideal. Had the same excellence of cancellation been found in all subjects studied, the dipole theory in its pure simplicity would have been considered amply proved. This, however, was not the case. There were other subjects, mainly patients, for whom it was difficult to find even one or two good cancellations, and the average (extrapolated) cancellation coefficient for all mirror pattern pairs located in normals was 0.09. This indicates, roughly speaking, that the dipole hypothesis is about 90 per cent good, when the central terminal with which the hypothesis is being tested is of the Wilson type.

It is important to note, in this connection, that the Wilson central terminal is not, in general, electrically neutral with respect to the heart's beat. Preliminary experience with a special central terminal derived from six contributing electrodes on the body surface, each contribution weighted in accordance with electrical distance from the heart, has shown that the Wilson terminal contributes a small finite voltage rather than a null to electrocardiographic readings. A new series of cancellation experiments using such a six-fold central terminal is planned, and is expected to show a limited degree of improvement in the cancellation coefficients obtainable.

The authors feel, however, that the most important thesis has already been established: that for most biologic purposes, the dipole hypothesis is a valuable one, and may be used in semiquantitative as well as in qualitative analyses.

SUMMARY

1. A procedure for determining accurately the degree to which electrocardiographic potentials may be ascribed to a dipolelike source has been experimentally evaluated. The method makes use of the cancellation properties of mirror patterns and has a sensitivity of approximately 2 per cent.

2. In a study of seventeen normal subjects and thirty-seven cardiac patients, mirror patterns were found along approximately 100 different anatomic axes through the heart, no direction giving significantly better mirror patterns than any other direction.

3. In general, approximately 90 per cent of the electrocardiographic potential appearing at any point on the body, including the precordial areas, may be ascribed to a dipolelike current source at the heart, in that only 9 per cent of any pair of mirror patterns, on the average, failed to cancel.

4. Although different points on the body are at different electrical distances from the heart, a study of bodily and cardiac dimensions failed to reveal any significant correlation between physical dimensions and electrical distance.

5. All of the studies were made using a Wilson central terminal. Since excellence of cancellation of mirror patterns depends on having a truly neutral central terminal as well as on having actual dipolelike activity of the heart, the Wilson terminal, accordingly, is shown to be quite satisfactory for leads in the anteroposterior direction as well as in the frontal plane. It was indicated, however, that careful derivation of a properly weighted central terminal might be expected to improve the degree of cancellation obtainable.

6. Since only a dipolelike source is capable of yielding mirror patterns in a wide variety of directions through the heart, the results obtained were taken to be a verification of the dipole theory for semiquantitative, as well as qualitative, purposes. The projection areas of the so-called Unipolar Electrocardiography must be regarded as having relatively little meaning.

REFERENCES

1. Grant, R. P.: Spatial Vector Electrocardiography. A Method for Calculating the Spatial Electrical Vectors of the Heart From Conventional Leads, Circulation **2**:576, 1950.
2. Duchosal, D. W., and Sulzer, R.: La Vectocardiography, Basle, 1949, S. Karger, p. 172.
3. Schmitt, O. H., Levine, R. B., and Simonson, E.: Electrocardiographic Mirror Pattern Studies. I. Experimental Validity Tests of the Dipole Hypothesis and of the Central Terminal Theory, AM. HEART J. **45**:416, 1953.

ELECTROSTETHOGRAPHY. III.

Crystal Microphone Characteristics at Low Frequencies for the Study of Cardiodynamics

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WE HAVE previously reported on the practical development of a pistonphone and its application to the calibration of microphones within the range of 10 to 1,000 cycles per second.[1] Although the pistonphone furnishes an absolute standard for calibration, its operation requires considerable skill and is time consuming. This report describes a secondary calibrator which is rapid in use and reports on the characteristics of a crystal microphone demonstrating its suitability for heart vibration studies.

Bauer furnished us with several telephone receivers and some of the details of their methods of calibration.[2] The receiver unit was clamped airtight to one end of a brass tube with an inside diameter of one inch and a volume of about 10 cubic centimeters. The microphone being tested was clamped to the other end using a rubber gasket of high elasticity. The receiver was driven by an audio oscillator and the power input measured by a rectifier type of milliammeter. Shure Bros. Inc.* calibrated their unit by substitution against their own reference standards; we used our pistonphone.[1] This secondary calibrator proved satisfactory, but the receiver units were not easily available. Furthermore, a receiver unit for this purpose should have maximum secular stability and, if possible, be manufactured to close tolerances. The Western Electric 716-A receiver unit was selected and obtained through the courtesy of the Northwestern Bell Telephone Company. This receiver is widely used in telephone headsets and is designed and manufactured for high stability and durability. Bell Telephone Laboratories reported that manufacturing tolerances were such that the output was constant within 2.5 decibels from 100 to 2,000 cycles and that there was negligible harmonic distortion up to 25 milliamperes input.[3]

Many variations in design are possible for the secondary calibrator. It is important that the air volume be sufficiently small so that resonance and echoes do not interfere; a volume of not over 15 c.c. allows ample margin for frequencies

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*Shure Brothers, Inc., Chicago, Ill.

up to 1,000 cycles per second. The assembly must be airtight. The scale reading on the rectifier milliammeter was adjusted using a suitable series resistance so that the meter read directly in dynes output per square centimeter. Figure 1 shows the microphone attached to the calibrator, the quick clamping device, and the meter in the background. The individual receiver units we used were considerably better than the over-all tolerance published, and over a three-year period the limiting factor in the accuracy of the secondary calibrator was that of the rectifier milliammeter, which is about 5 per cent.

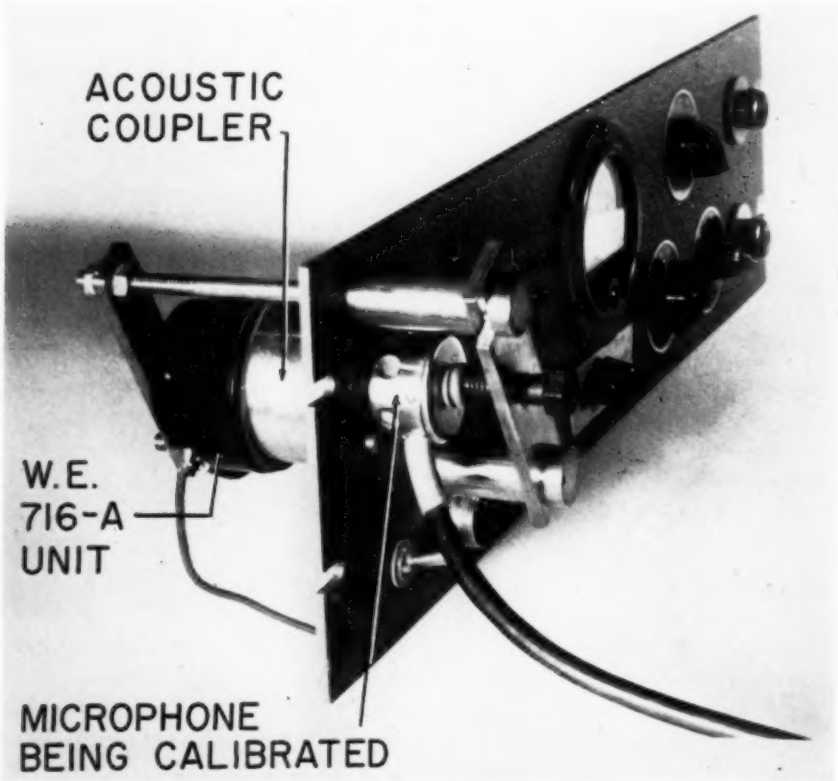

Fig. 1.

Although a number of different types of microphones were tested the Shure 66D was selected for the frequency range of 20 to 1,000 cycles per second. To determine reliability and conditions of operation, seven 66D microphones were studied over a period of two years. Both the pistonphone and the secondary calibrators just described were used as sources of power. The microphone output was measured with a push-pull resistance capacity-coupled amplifier and cathode ray tube using a substitution technique. The deflection on the cathode ray tube was first determined by a divider, and then a known voltage from the audio oscillator giving the same deflection was substituted for the microphone output. Due to the small capacity of the 66D microphone the grid resistors on the input stages were 10 megohms to extend the low frequency response.

Over the range of 20 to 1,000 cycles the shape of the output curves of all seven microphones when driven by a constant dyne input was essentially alike. The shape of the output curve did not change over the two-year period even in the case of P-2524 which was reduced 50 per cent in sensitivity over a 23-month period. Output curves of D-6 on Dec. 18, 1949 and on Feb. 9, 1952 are illustrated in Fig. 2. Under the conditions of calibration, the output is constant over the range of 30 to 600 cycles. The reduction in output at 20 cycles is slight. Over 600 cycles the output increases, amounting to less than a 10 per cent increase at 800 cycles. The shape of this rise to 1,000 cycles is similar for all seven microphones, and above 1,200 cycles there is microphone variation with sharp maxima in the region of 1,500 and 2,000 cycles. The position of these peaks depends upon details of the crystal mounting. The microphones thus have an essentially linear range to 800 cycles and a useful, that is predictable, range to 1,000 cycles. We have not used them for this work above 1,000 cycles per second.

Table I shows the dynes per square centimeter for a millivolt output at 100 cycles per second for all microphones during the period of test. D-1 and P-2524 showed loss in sensitivity and were both over four years old without crystal replacement. Until the summer of 1951, the microphones were kept in the room environment. At that time during a period of high humidity, several lost sensitivity of over 10 per cent within a week. This loss was temporary. Since that time the microphones have been kept in tight polyethylene bags with Davison Silica gel air dryers which provide a 50 per cent humidity in which the crystal and its protective coating have maximum stability. The data in Table I were not corrected for temperature variations since temperature tests were made on only four microphones.

TABLE I. DYNES PER SQUARE CENTIMETER REQUIRED FOR 1 MILLIVOLT OUTPUT

DATE	D-1	D-2	D-5	D-6	P-2560	P-2524	M-2135
12/ 5/49	6.35	7.6	8.7	7.3	14.6		17.5
12/18/49	6.9	6.35	9.0	8.2	14.5		15.9
3/18/50	6.17		8.7		15.9	18.9	
4/16/50	6.35	6.8	9.0	8.2	16.0	15.4	18.1
7/17/50	6.35	6.1	8.7		13.6	16.0	17.3
2/10/52	10.6	6.96	11.1	9.3		35.7	58.0

The outputs of the microphones were proportional to the dynes input, and this is illustrated in Fig. 3 for microphone P-2560. The upward bow of the output curve for forces of 100 and 150 dynes per square centimeter was due to impedance mismatch between the audio oscillator and the 716-A receiver, and since the energies derived from the precordium are below 25 dynes, it was not necessary to correct this mismatch for our calibration purposes.

The type of crystal used in the 66D microphone is affected by temperature. Figure 4 shows that the curve shape is not affected by temperature variations from 15° to 35° Centigrade. The various curves illustrated are for a single microphone. The variations in output at 100 cycles per second for four microphones

are shown in Fig. 5, and Fig. 6 shows the variation in crystal capacity. These measurements were made using an air thermostat held to less than 0.1° C. variation and allowing ample time for equilibrium to be reached for each measurement.

In precordial studies, the microphone button is in direct contact except for a layer of elastic rubber.[4] The method of calibration described utilizes compression and refraction of air to transfer the forces to the sensitive portion of the microphone. Both air compression or the interposition of elastic rubber between driver and microphone are accepted practice in acoustic or vibration calibration.

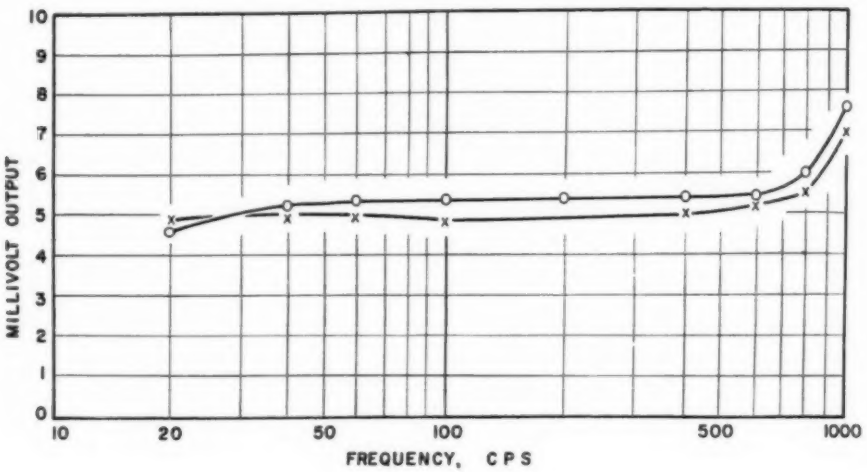

Fig. 2.

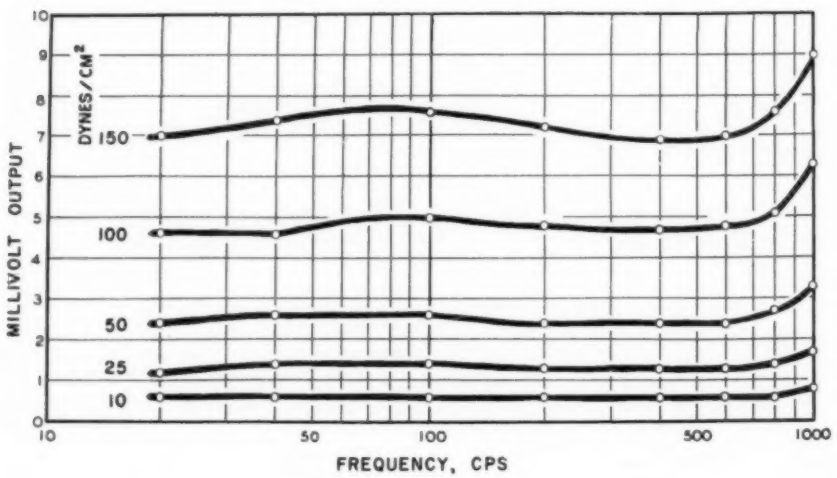

Fig. 3.

The crystal in the 66D microphone is a small flat rectangle and is mounted with opposite sides attached to the microphone frame and the sensitive button respectively. The question could be raised as to possible abnormal patterns being produced by the microphone in cases of emaciation or radical mastectomy in which only a small area of the sensitive button might be in contact. Such pat-

terns would belong to the complex group of vibrating patterns seen when plates are oscillated in various segments. Tests by us showed that if a vibrating point (less than 1 mm. in diameter) was used to explore the sensitive button then abnormal patterns could be produced, that is the movement of the vibrating point was not reproduced. However, if the point was broadened to 0.5 cm. this variation disappeared. The distortion also disappeared if a thin layer of rubber was interposed between point and sensitive button. This layer of rubber is standard

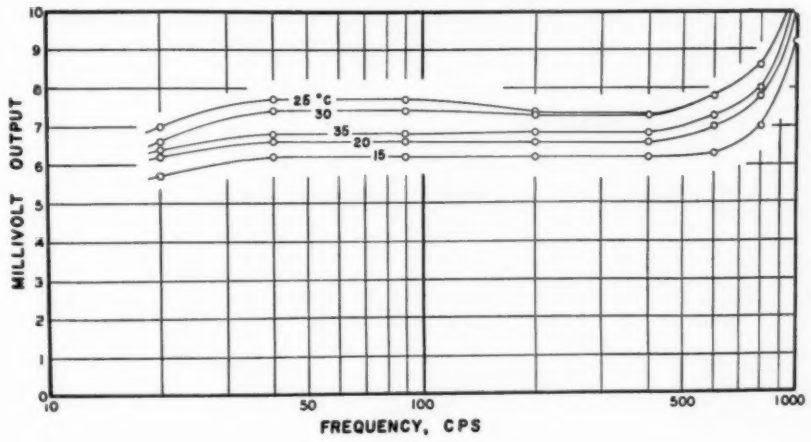

Fig. 4.

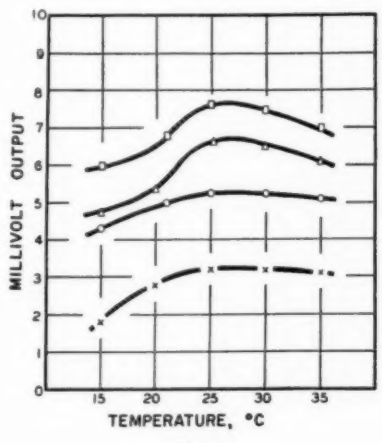

Fig. 5.

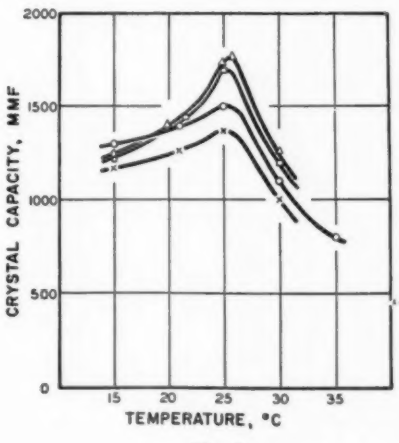

Fig. 6.

on all 66D crystal microphones and in addition we have cemented a small elastic rubber disc about 1.5 cm. in diameter and 3 mm. thick to the microphone. Actual crystal movements at the levels used in precordial studies are very small, and some attempts by us at optical measurements indicated that the movement is not over a few hundred thousandths of an inch.

The method of secondary calibration described is independent of temperature and changes in the output of the microphone and is based upon the constancy of

the shape of the frequency-output curves of the microphones studied and upon the stability of the 716-A receiver unit and millimeter. At the present time the rectifier type of milliammeter is the limiting factor which can be held to about 5 per cent. The pistonphone calibrations are actually based on peak deflections, and although the milliammeter is calibrated to read in dynes, its construction is that of a high inertia electromagnetic meter so that the deflection varies with frequency. This frequency effect can be avoided by using a cathode ray tube and a substitution technique for measurement, but such accuracy is unnecessary in precordial cardiodynamics at the present time because of the variations resulting from the pickup between precordium and microphone.

REFERENCES

1. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Microphone Calibration at Low Frequencies in Absolute Units, Rev. Scient. Instruments. (In press.)
2. Bauer, B. B., Shure Bros. Inc., Chicago, Ill. Personal communication.
3. Jones, W. C.: Instrments for the New Telephone Sets, Bell System Technical Journal **17**:338, 1938.
4. Dunn, F. Lowell, and Rahm, Walter E., Jr.: Electrostethography. II. A New Method for the Study of the Precordial Transmission of Cardiodynamics, Am. Heart J. **44**:95, 1952.

THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF SEPTAL INFARCTIONS

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THE ELECTRICAL phenomena of the interventricular septum have not been studied extensively and in most of the published electrocardiographic papers these phenomena have been accorded only minimal importance. So little is known about the electrocardiographic changes set up by septal infarcts, that recently Levy and Hymann[1] stated the following: "there are certain regions of the myocardium in which the absence of activation, due to dead muscle, does not cause appreciable changes in the standard or in the six precordial leads; one of these sites is the interventricular septum."

The evidences which are at present most generally accepted as suggestive of septal involvement are as follows:

1. The presence of extensive infarctions in the anterior or posterior wall of the heart.[2,5,7]
2. A QS complex from V_1 to V_4, or the absence of R in any of the Leads V_2, V_3, or V_4, if in the adjacent leads there is an initial positivity.[5-7]
3. The presence of Q in V_5 and V_6 when there is a complete block of the left branch of the bundle of His, and the notation of this wave in the right precordial leads when there is a block of the right branch. These findings were presented by Wilson[9,10] and have been confirmed by other authors.[5,11,12,14,15]

It is well-known that the morphology of unipolar tracings does not change across a transmural dead electrical zone of the free ventricular wall, that is, the unipolar tracings obtained at the epicardial region of the damaged zone are similar to those obtained at the endocardial surface of the same zone. Recently, Sodi-Pallares and associates[14,15] emphasized that the morphology of the unipolar leads obtained on the surface of the septum in cases of left bundle branch block, can be registered in the precordial leads if the exploring electrode is facing a dead zone of the free ventricular wall, and that, on the other hand, in cases of destruction of some portions of the septum, the exploring electrode is oriented to the new boundaries of the undamaged septal areas. The tracings obtained in the precordial leads of human cases in certain infarctions of the myocardium are very similar, morphologically, to the unipolar tracings, described by the same authors, on the septal surfaces and within the septal mass of a dog's heart.

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The similarity of the intracavity, precordial and epicardial tracings[14,16] obtained in both dog and human hearts, enables us to apply to the human heart the conclusions derived from dog hearts.

In Figs. 1, 2, and 3 tracings found in different portions of the septal surfaces are shown in accord with the publications mentioned above. With these new ideas, we studied septal infarctions from an anatomic and electrical viewpoint, using necropsy material of the Instituto Nacional de Cardiología. The cases were divided into two groups: (1) cases without bundle branch block and (2) cases with bundle branch block.

In each of these there were subgroups, in accordance with the degree and the extent of the infarction in the interventricular septum.

It is important to point out that in this investigation we are concerned exclusively with electrical changes corresponding to dead electrical zones, that is to changes in the QRS complex. The changes in RS-T and T help to solve the diagnostic problem, especially in cases of recent infarctions.

I. CASES WITHOUT BUNDLE BRANCH BLOCK

Of the forty-two cases studied, only eight were not complicated with bundle branch block. In accordance with the extension of the septal damage, three principal subgroups can be formed:

A. *Massive Infarction of the Septum.*—

We use this term to designate infarctions which involve more than two-thirds of the septal mass. We do not speak of destruction of the whole septum, because we have not found in the literature, or in our own cases, a lesion this extensive. There is always a spared portion of the septum, and even in the largest infarcts which we studied, this portion approximated a quarter of the septal mass.

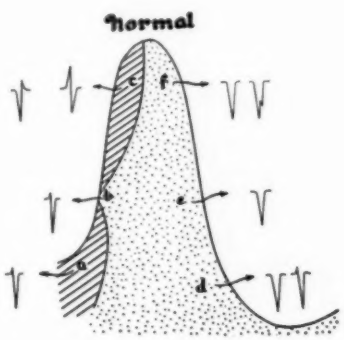
Massive destruction of the interventricular septum (Fig. 4) would determine, theoretically, the disappearance of the Q wave in the left precordial leads and the diminution or disappearance of the R wave in the right precordial leads, due to the lack of the first vector of septal activation; this possibility has been pointed out by Levy and Hymann.[1] Supposing that the free wall of the left ventricle is not damaged, it would be logical to expect an increase of voltage in the R wave in Leads V_5 and V_6, because of the disappearance of the late septal opposing vectors.[12] This condition was not encountered in our series, since in almost all cases there is a greater or lesser extension of the infarct to the free wall of the left ventricle.

The R wave in the right precordial leads may persist, since it remains the activation of the free wall of the right ventricle. The place where theoretically there ought to appear a QS complex is in the intermediate leads (V_3 to V_4) that are oriented toward the infarcted septal zone. Even in those cases in which the high portion of the septum may be spared (the upper one-third), the orientation of the electrode toward the infarcted area permits the recording of the QS complex; only when there is a small spared zone in the septum near the epicardial surface of the anterior wall is it possible to register a small R wave of less voltage than the R of the right ventricle. The diminution of the R of V_1 to V_3 to V_4 is a finding that al-

ready has been pointed out by Wilson[3,4] as a sign of septal infarction. In the majority of the cases the infarction involves more or less the free wall of the left ventricle.

The electrocardiogram in Fig. 5 shows the lessening of the R wave in V_2 to V_3 and from V_3 to V_4. In V_5, V_6, LI and V_L there are QS complexes that suggest important damage to the lateral portion of the free wall of the left ventricle. The autopsy showed an enormous infarction that involved the entire lower one-half of the left ventricle and the inferior two-thirds of the interventricular septum.

Fig. 1.



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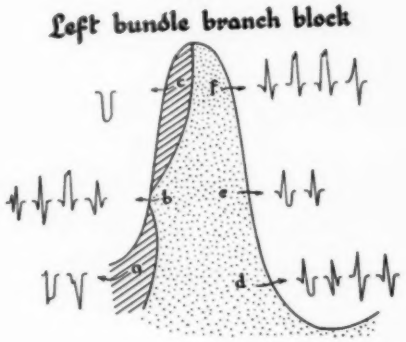

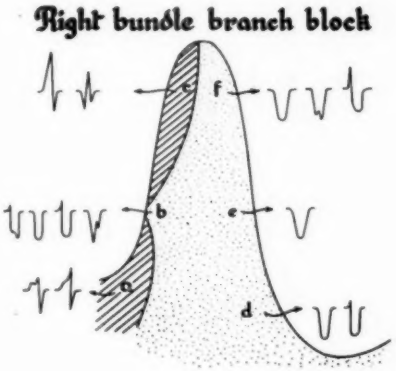

Fig. 3.

Fig. 4.

Fig. 1.—Morphology of unipolar leads, obtained in distinct portions of the interventricular septum of the dog's heart under controlled conditions.

Fig. 2.—Morphology of unipolar leads obtained in distinct portions of the interventricular septum of the dog's heart, after cutting the left branch of the bundle of His.

Fig. 3.—Morphology of unipolar leads obtained in distinct portions of the interventricular septum of the dog's heart, after cutting the right branch of the bundle of His.

Fig. 4.—An explanation for the morphology obtained in the precordial leads in the presence of massive infarction of the septum, when there is no bundle branch block.

If the massive infarction of the septum is accompanied by widespread damage of the free wall of the left ventricle, one can expect diminution of the voltage of the ventricular complexes and, more important, the presence of QS complexes in all the precordial leads (Fig. 6). This seems to be the most frequent picture in this type of infarction.

The electrocardiogram in Fig. 7 shows rapid ventricular complexes, essentially negative, in all the precordial leads and in LII, LIII and V_F. It is not possible to rule out a small degree of incomplete left bundle branch block. The initial slurring in the upstroke of the R wave in the LI and V_L reinforce that possibility. Also the very tiny initial positivity in V_6 speaks in favor of that possibility, especially if the infarction is transmural. It suggests an extensive necrotic zone both anterior and posterior with extensive damage to the interventricular septum. The pathologic findings were the following: ". . . the lower three-fourths of the interventricular septum presented extensive necrosis and this necrosis extended to the free wall of the left ventricle to an extent of 4.5 cms. from the apex."

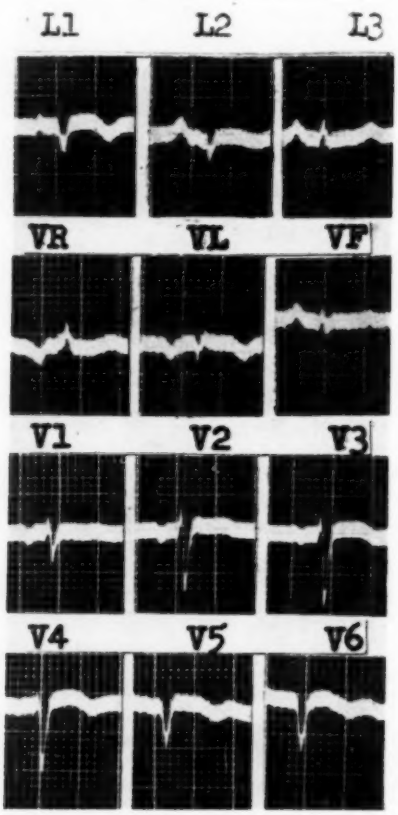

Fig. 5.—The electrocardiogram of a patient in which the autopsy showed an infarction that involved the lower two-thirds of the septum and the lower one-half of the left ventricle.

B. *Infarctions of the Lower One-third of the Septum.*—

When the infarction of the lower one-third of the septum is transmural we should expect findings similar to those for a massive infarction of the septum. That is, in this type of infarction, theoretically, the initial negativity should be able to decrease or disappear in the left ventricle, with a consequent diminution of the R wave of the right ventricle. This condition of infarction across the wall

of the inferior one-third of the septum without damage of the free ventricular wall was not encountered in our series.

Similarly, important damage of the free wall of the left ventricle complicating this type of septal infarct explains the presence of QS complexes in almost all the precordial leads.

It is very difficult to differentiate a massive infarction of the septum from an infarction, equally transmural, located in the lower one-third of the septum. In the electrocardiogram of Fig. 8, one can see the R waves in the right precordial Leads V_1 to V_2, QS complexes in V_3, V_4 and V_5, and QR in V_6. This tracing suggests an infarction of the lower portions of the septum plus damage of the free wall of the left ventricle. It is very difficult to determine the height of the necrotic zone in the septum. The necropsy report was as follows: ". . . infarction which involves the lower one-third of the interventricular septum, the apex, and the anterior and posterior walls of the left ventricle."

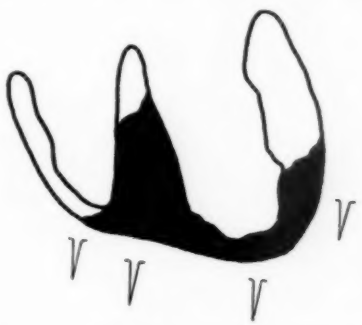

Fig. 6.—Morphology of the unipolar leads in a massive infarction of the septum with extensive damage of the free wall of the left ventricle, without bundle branch block.

Apparently, there is no close relationship between the degree of involvement of the free wall of the left ventricle and the extension of the infarct into the septum. Massive septal infarction may be accompanied by only slight damage to the free wall.

In some cases with extensive infarction of the interventricular septum, Qr or qr complexes may be seen in the right precordial leads. It appears to be an indispensable theoretical condition to obtain this type of tracing, that the superior one-third be spared, and that there be an involvement, of greater or lesser importance, of the free wall of the right ventricle. Such tracings can also suggest right atrial dilatation without any myocardial infarction.[18] (Fig. 9).

The possibility of a misleading picture of dilatation of the right atrium[18] in a case of myocardial septal infarction is seen in Fig. 4. This calls attention to the low voltage of the QRS complex in all the leads, and, on the other hand, the presence of qr complexes in V_1 and V_2, which can correspond to an increase in size of the right atrium. This increase in size of the right atrium could not be proved radiographically, and on the other hand, was not seen at the autopsy. In addition, the electrocardiogram is suggestive of an incomplete block of the right branch (slurred S wave in LI, V_L, V_5 and V_6). Once we have discarded a dilatation of the right atrium, we believe that the most likely explanation for the

qr complexes of V_1 and V_2 is that the exploring electrode is oriented to the high portions of the septum which are the only areas spared by the infarction. The Q wave of LII, LIII and V_F strengthens the diagnosis of infarction of the lower portions of the septum. The slurred Q wave in LIII makes one suspect a posterior infarction. This last possibility was corroborated at the autopsy: ". . . an extensive infarction of the interventricular septum which extends from the posterior border anteriorly, sparing only the anterosuperior portion of the septal muscle; in addition, there are extensive necrotic zones in both ventricles, mainly in the right ventricle."

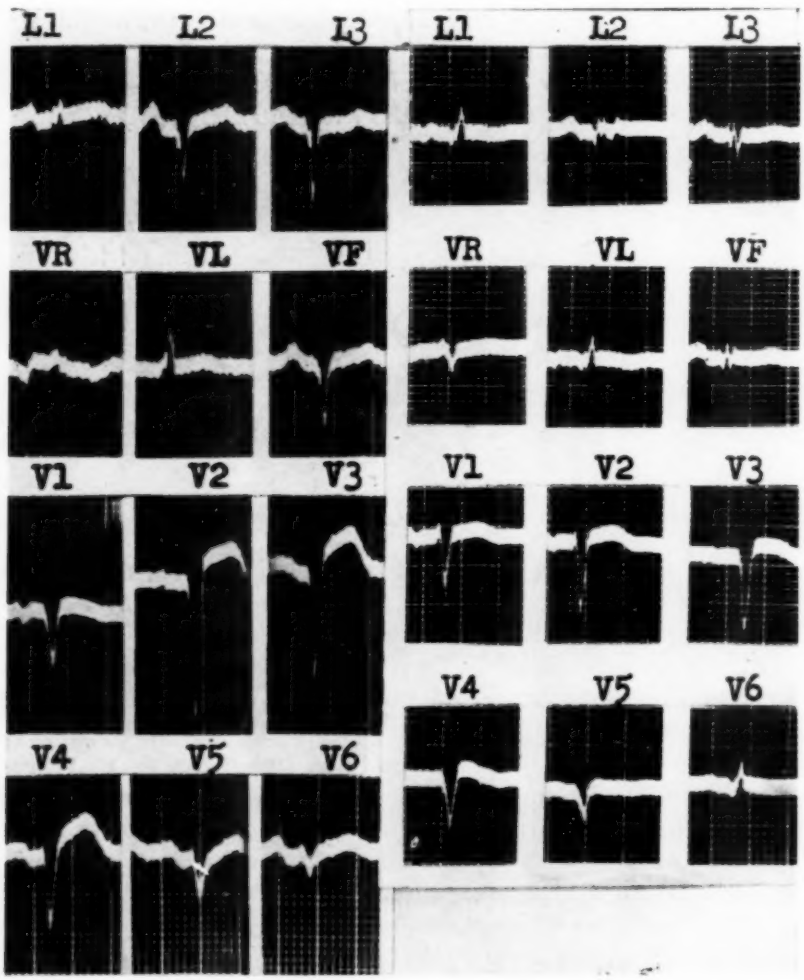

Fig. 7. Fig. 8.

Fig. 7.—Note the presence of essentially negative complexes in all precordial leads in LII, LIII and V_F. The autopsy showed an infarction of three-fourths of the interventricular septum, and extending into the inferior portion of the free wall of the left ventricle.

Fig. 8.—The autopsy in this case showed an infarction of the lower one-third of the interventricular septum. The electrocardiogram shows the difficulty in determining the height of septal necrosis.

C. *Infarctions of the Superior One-third of the Septum.*—

Infarctions limited to the superior one-third of the septum are difficult to analyze. Theoretically, one can expect an increase in voltage of the R wave in the precordial leads oriented toward the left ventricle because of the disappearance of the last septal vectors which oppose the activation of the free wall of the left ventricle. This finding is extremely difficult to evaluate, especially in patients with other complications, such as left ventricular hypertrophy, abnormal conduction, etc., which are in themselves capable of causing this increase in voltage. In our series, this condition was not encountered when bundle branch block was absent.

II. CASES WITH BUNDLE BRANCH BLOCK

The literature contains many papers pointing out the high incidence of bundle branch block, and in our series a left bundle branch block was the more frequent complication of septal infaction.

Master and associates[19] have shown that in some cases the only evidence of septal infarct may be an alteration of intraventricular conduction which appears suddenly. On the other hand, most authors agree that a left bundle branch block hides the evidence of a myocardial infarction, with the exception of those cases which show a Q wave in the left precordial leads.

Fig. 9.—Unipolar tracing in a case of extensive septal infarction with involvement of the free wall of the right ventricle.

Conversely, we have seen that, when the septal infarct is large, the presence of left bundle branch block helps to make the diagnosis and often helps to establish its extension in height, which is practically impossible when there is no alteration of conduction. Let us consider first:

A. *Massive Infaction of the Septum Complicated by Left Bundle Branch Block* (*Fig. 11*).—

The first sign of importance is the presence of Q waves in the leads oriented toward the left ventricle. This finding is of value both in a complete block and in an incomplete block, although it should be noted that the presence of the Q wave is of greater diagnostic importance when the block is complete. The magnitude and the duration of the Q wave vary in relation with the septal damage and can be utilized as an indication of the upward extension of this damage.

We also consider as a finding of great significance the presence of QrS complexes in V_3, V_4, V_5, when there is a left bundle branch block. These complexes are the result of the orientation of the exploring electrode toward the high spared regions in the interventricular septum. In those cases in which these spared zones are small, essentially negative complexes will be found in the same leads.

There may be an initial R wave in the right precordial leads which corresponds to the activation of the free wall of the right ventricle.

The electrocardiogram corresponding to Fig. 12 shows a complete left bundle branch block. There is a wide Q wave in LI, V_L, and V_6 and a complex of the QRS type in V_5. Also there is diminution of the R wave from V_2 to V_1 and the

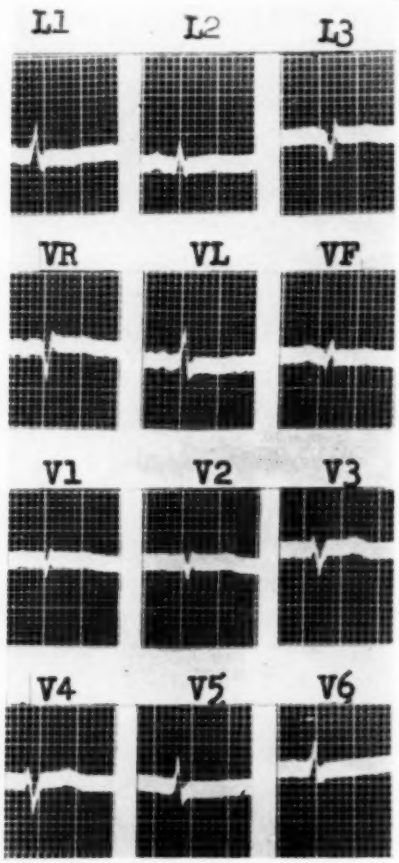

Fig. 10.—Showing qr type complexes in V_1 and V_2 which probably correspond to a high spared septal region, in the presence of an infarction which significantly involved the interventricular septum and both free ventricular walls, especially that of the right.

complex in V_4 is predominantly negative with notching and slurring. These findings suggest a septal infarction mainly of the lower portions of the septum; the presence of a high R wave in LI, V_L and V_6 suggests that the free wall of the left ventricle has not suffered important damage. The autopsy showed: ". . . the infarction is extensive in the septum, from the anterior portion to the posterior. Posteriorly the damage involves the insertion of the septum, in the inferior third of

the posterior face of the left ventricle, and in the forward extension, the superior border of the infarction rises, reaching the anterior border to within 2 cm. below the aortic semilunar valves. It involves the free wall of the left ventricle only in the zone corresponding to the septal infarction, extending in this region to within 1 cm. of the epicardium."

When the free wall of the left ventricle is extensively damaged (Fig. 13), the exploring electrode oriented toward the lateral infarcted face of the ventricle, shows a tracing similar to that recorded in the left ventricular cavity, which in these conditions of left block with septal infarction is of the QrS type. In the spared zones of the lateral face of the left ventricle the ventricular complex is of the qR type.

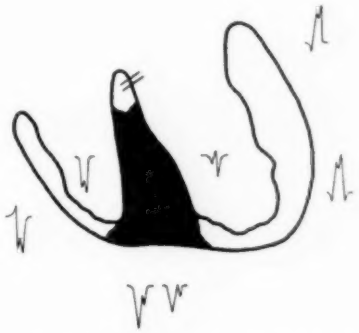

Fig. 11.—An explanation for the morphology of precordial leads in the presence of a left bundle branch block and massive infarction of the interventricular septum.

Figure 14 shows the condition previously described. There is a complete left bundle branch block and a Q wave in LI and V_L; there is an obvious diminution of R in V_3 to V_4, with an essentially negative complex in V_4, a W complex (Qrs) in V_5 and a qRs in V_6. The persistence of S to V_6 suggests damage of the free wall of the left ventricle. The absence of S in LI and V_L suggests that the infarction spares the lateral high portion of the free wall of the left ventricle. The necropsy findings of this case were the following: "The myocardium contains an extensive scar that involves almost all of the anterior face of the left ventricle, leaving a spared wedge in the superior external portion of the free wall of the left ventricle. The infarction involves the anterior two-thirds of the septum and shows calcification of the septal apex."

The importance of recognizing partial left bundle branch block in making the diagnosis of septal infarction is seen in the case represented by Fig. 15. If we suppose that we do not have an incomplete left bundle branch block, the presence of Q in LI, V_L, V_5 and V_6, and of the complex W in LII, would suggest an anterolateral infarction of the free wall of the left ventricle that would have large extensions to the endocardium without reaching the epicardium; a diagnosis of septal infarction would be practically impossible since the only evidence for this could be a diminution of R of V_3 to V_4. This evidence is not conclusive.

If, however, in this tracing we attribute the slurring of the R wave in LI, V_L and V_6 to an incomplete left bundle branch block,[21] the presence of the Q wave in the same leads could be considered as evidence of an important septal infarc-

tion. The necropsy report in this case stated: ". . . the infarction destroys the septum in width and depth, from the junction of the superior one-third with the middle one-third, to the inferior portion of the left ventricle. Both the septum and the inferior portion of the left ventricle contain two fibrous layers, in the middle of which are seen completely necrotic muscular masses. In addition there is a hole in the septum, obliterated by a thrombus, comunicating with both ventricles."

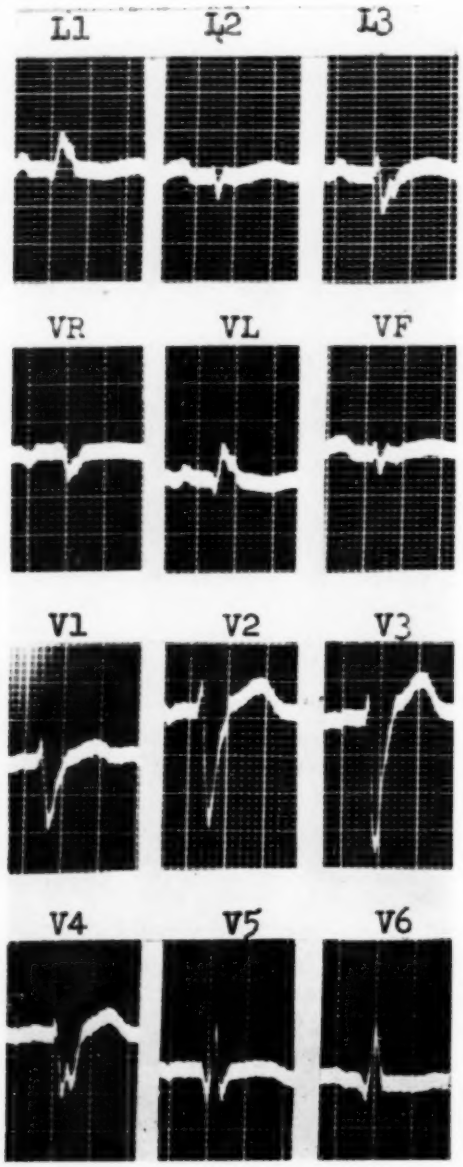

Fig. 12.—Left bundle branch block. There are Q waves in LI, V_L and V_6. QRS type complexes in V_5; frank diminution of R in V_2 to V_4, being the rapid ventricular complex in V_4, essentially negative. The autopsy showed an infarction of the inferior two-thirds of the septum that spared the posteriorsuperior region. The free ventricular wall was involved only in the region of the septal insertion.

This tracing is of great value in demonstrating the importance of abnormalities of conduction in the diagnosis of septal infarction even though it may be an incomplete block.

B. *Infarction of the Inferior One-third of the Septum, Complicated by Left Bundle Branch Block (Fig. 16).*—

When the infarction is located in the lower one-third of the septum and is transmural the following findings occur: (1) there are no QS complexes; (2) there are qRs complexes in the leads oriented to the septum (V_2 to V_4), but the R wave is of greater magnitude than when the infarction involves the lower two-thirds (the complexes then are qRs and not QrS). (3) There appears a Q wave in the left precordial leads, but of less magnitude and duration than with a more extensive infarction. This means that the degree of wave positivity in the leads oriented to the septum appears to vary with the extension of the septal mass involved by the infarction.

Left bundle branch block determines the appearance of positive deflections in the left septal mass; the complexes can be Rs, qRs, qrS, at times qR (Fig. 16). After experimental production of a left bundle branch block, the unipolar leads recorded at the septum show (Fig. 16) that as we ascend the septal mass with the

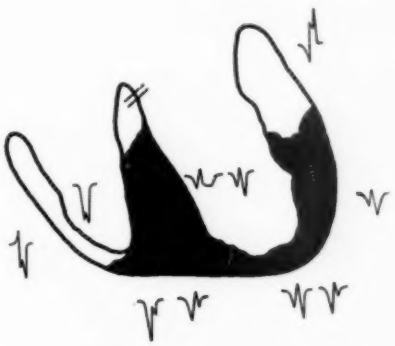

Fig. 13.—Morphology of the unipolar leads in the presence of left bundle branch block and massive infarction of the interventricular septum that significantly involved the free wall of the left ventricle.

exploring electrode, the positive wave increases in magnitude and becomes more slurred. The slurred R wave is the result of abnormal septal activation, from right to left and from below upwards. This R wave decreases in voltage when an infarction destroys the lower inferior one-third of the septum and practically disappears in cases of massive septal infarction. The leads oriented to the infarct in the lower portion of the septum and those oriented to the free wall of the left ventricle will register a negative initial deflection with notchings and slurrings. This corresponds to the initial normal negativity of the intact septal mass. In other words these leads are oriented to those septal regions at the beginning of the cardiac cycle. The magnitude of the Q wave increases proportionally with the size of the infarcted mass.

The electrocardiogram in Fig. 17 corresponds to a case in which the autopsy report stated: "The heart is considerably enlarged, the anterior face is composed

exclusively of right ventricle, the left ventricle occupies the posterior face. The infarction is found in the inferior one-third of the septum." The electrocardiogram shows incomplete left bundle branch block and complexes rsrS in V_5 and qrs in V_6; moreover, there is a decrease of R from V_3 to V_5. Because of the heart's position, as evidenced by necropsy, the unipolar recordings from V_1 to V_4 registered fundamentally the potential from the right ventricle and in V_5 and V_6 the electrode was oriented to the inferior septal mass. Therefore, these qrS

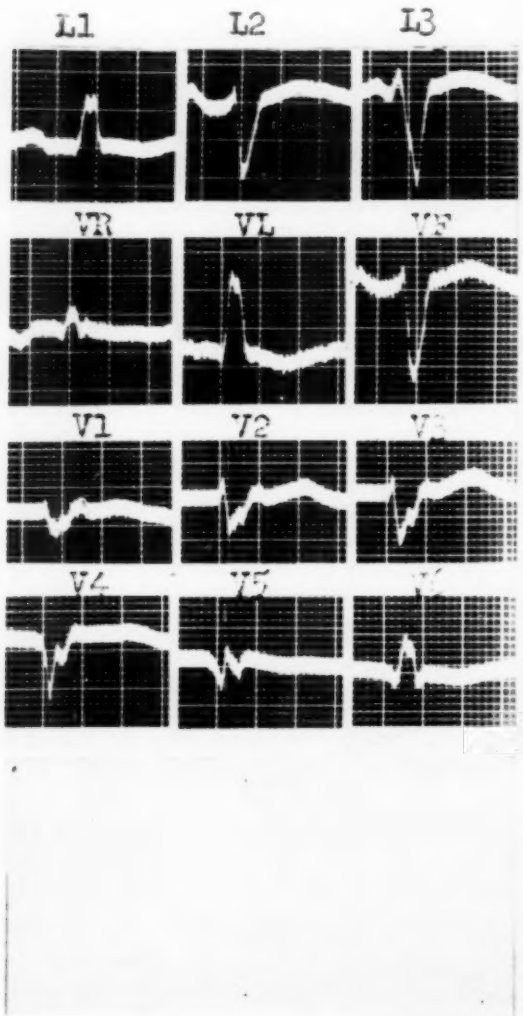

Fig. 14.

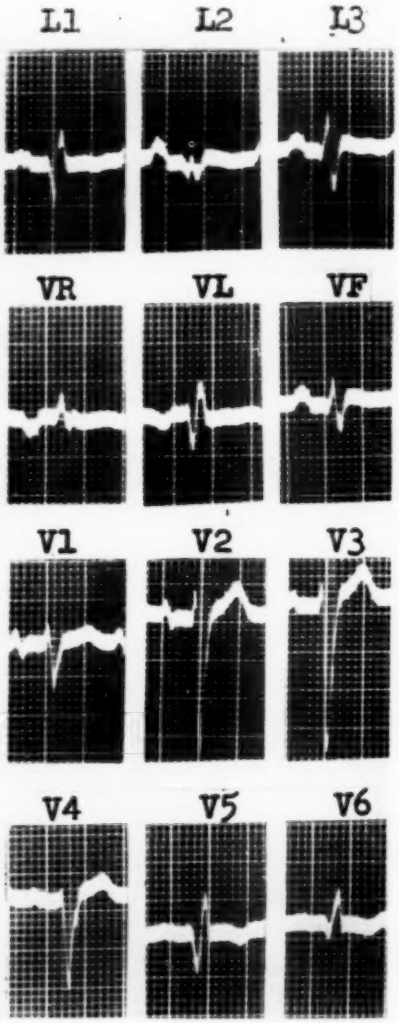

Fig. 15.

Fig. 14.—The electrocardiogram suggests complete left bundle branch block and extensive septal infarction that spares the superior portion; in addition it suggests damage of the free wall of the left ventricle without involvement of the high region in the same free wall.

Fig. 15.—A demonstration of the importance of recognizing a small degree of left bundle branch block in making the diagnosis of septal damage. In effect there is Q wave in LI, V_L, V_5 and V_6 in the presence of a slurred R wave in the same leads and W complexes in LII. At the autopsy there was found a massive infarction of the septum and of the inferior portion of the left ventricle.

complexes may be interpreted as corresponding to incomplete left bundle branch block with low septal infarction.

When the involvement of the inferior portion of the septum is of minor extent, the initial negative deflections are correspondingly of small magnitude, as can be seen in the electrocardiogram of Fig. 18. The autopsy in this case showed an infarction of the apex of the left ventricle and of the inferior portion of the septum, which, however, did not involve the whole inferior one-third of the septum. The tracing showed an incomplete left bundle branch block with qRs complexes in V_4 and V_5. These alterations are difficult to evaluate since in incomplete blocks we may find a Q wave in the left precordial leads.[21] Nevertheless, there are Q and S waves in the same lead and the magnitude of Q looks greater in V_4 and in V_5 than in V_6. We believe that a similar tracing, in the presence of incomplete left bundle branch block, ought to suggest the possibility of low septal infarction with small invasion of the free wall of the left ventricle, since the S wave is of small magnitude.

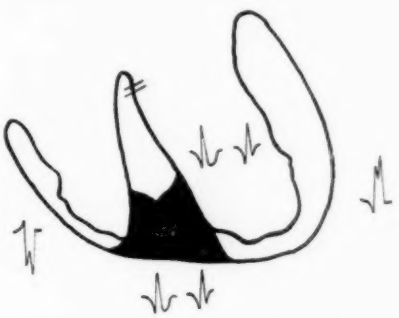

Fig. 16. Morphology of the unipolar leads in a case of infarction of the inferior one-third of the septum with left bundle branch block.

In case the infarcted zone also extends to the free wall of the left ventricle, qRs complexes can be registered in V_5 and V_6. These complexes are the transmission of the left intraventricular morphology when the left bundle branch block is associated with destruction of the inferior portion of the septum, a condition similar to that which we have illustrated in the massive infarctions of the septum. We have pointed out that the voltage and duration of the Q wave are approximately related to the extension of the interventricular septal infarction. The extension of the infarction to the free ventricular left wall is, on the other hand, related to the magnitude of the S waves in the left precordial leads. This finding does not seem to agree with the classical ideas. Nevertheless, in cases of septal infarction with left bundle branch block, the unipolar tracing recorded in the left ventricular cavity (Fig. 20) is of the qRS type in which the S wave is mainly due to the last septal forces oriented upwards. If there is not infarction of the free left ventricular wall, the activation forces of the same wall, very much delayed by the conduction defect, hide the S wave. On the other hand, if there is a transmural infarction, the intracavity potential variation is transmitted and an S wave is registered. The occurrence of this in several leads should suggest an important extension of the transmural infarction into the free left ventricular wall.

Sodi-Pallares and Rodriguez[14] have encountered complexes of the qRs, qR and even of the rsRs types, in the superior portions of the left septal mass in the presence of left bundle branch block. There exists the possibility that this morphology can be registered in the right precordial leads V_1 and V_2, when the infarcted tissue extends to the inferior portion of the septum, to the right septal areas, and to the trabecular regions of the free wall of the right ventricle. Those morphologies may lead to erroneous diagnosis of right bundle branch block. Nevertheless, in these cases the left bundle branch block is recognized by the peripheral leads (especially LI and V_L) and by high left precordial leads.

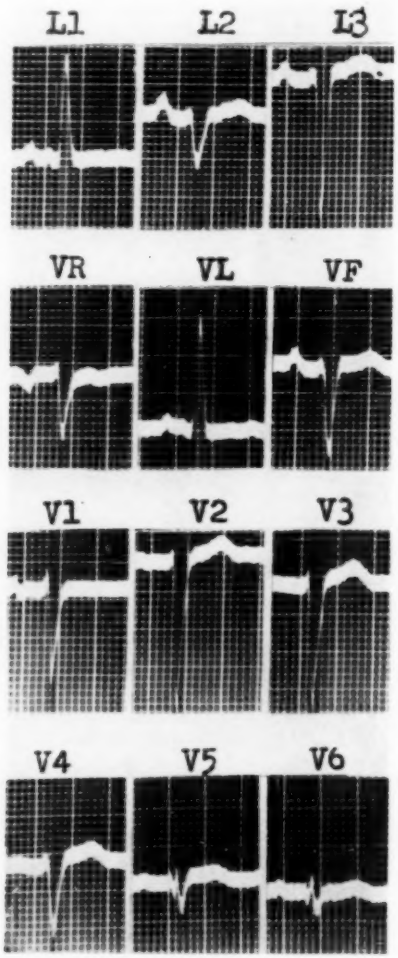

Fig. 17. Electrocardiogram in an infarction of the lower one-third of the interventricular septum. Note the qrs type complexes in V_6. The anatomic position of the heart in this case resulted in tracings of right ventricular morphology from V_1 to V_4; the transitional zone is displaced to the left and is seen in V_5 and V_6.

The above considerations are seen in the case corresponding to Fig. 19. The Leads LI, V_L, and V_6 suggest a left bundle branch block complicated by a low septal infarction and probably by infarction of the lateral face of the left ven-

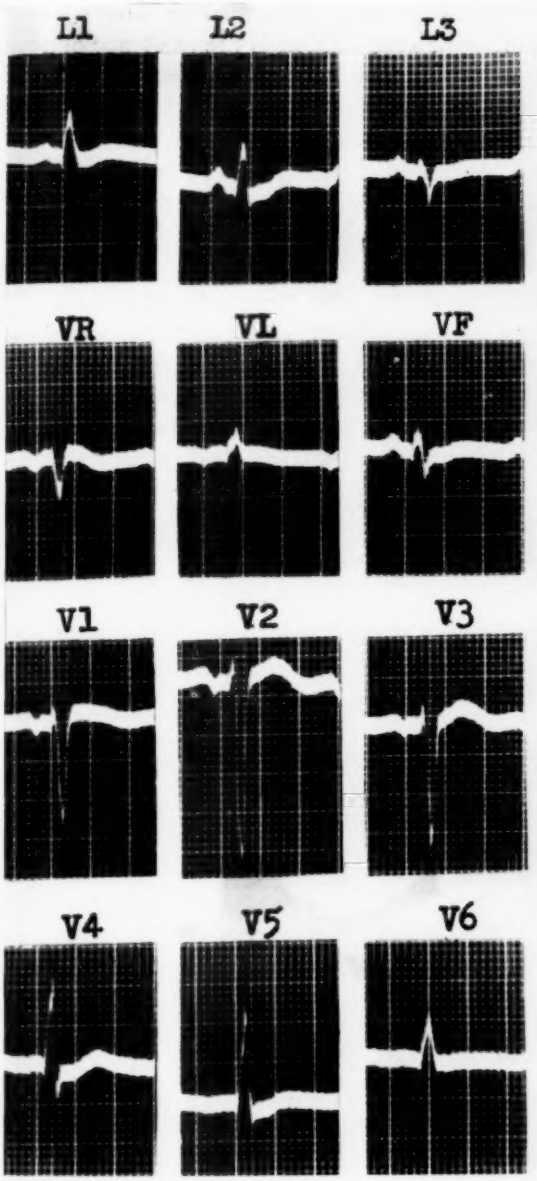

Fig. 18.

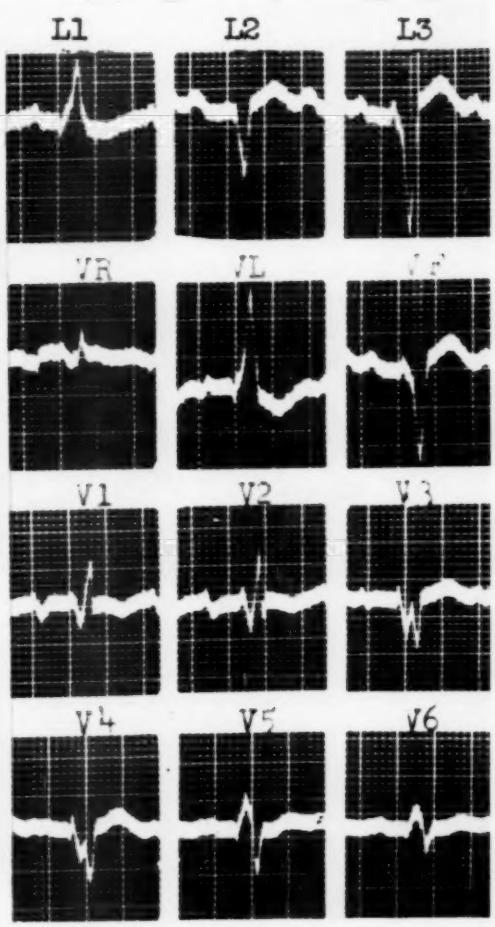

Fig. 19.

Fig. 18.—Shows left bundle branch block with qRs type complexes in V_5 and V_6. This tracing demonstrates the fact that when the involvement of the inferior portion of the septum is small the Q wave is also small and difficult to evaluate and the voltage of R is practically undiminished. At the autopsy there was found an infarction of the apex of the left ventricle and of the inferior portion of the septum which, however, did not involve the whole inferior one-third.

Fig. 19.—Infarction of the inferior one-third of the interventricular septum and of the antero-superior region of the same. From these leads, oriented toward the left ventricle, we can suspect a complete left bundle branch block complicated by an infarction of the septum and of the free wall of the left ventricle. Nevertheless, the right precordial leads, V_1 and V_2 provide suspicion of an alteration of conduction of the right side, unless it is assumed that the complexes of these leads correspond to the transmission of unipolar high septal morphology in the presence of left bundle branch block and low septal infarction.

tricle; the V_3 and V_4 leads might help this suspicion. Nevertheless, Leads V_1 and V_2 lend themselves to two different interpretations. One is the existence of a right bundle branch block, in which case it would be impossible to explain the morphology of the remaining leads, especially the slurred R wave in V_5 and V_6, unless we admit of an alteration of conduction of both bundle branches. The other would be that we accepted that the block was of the left side, in which case the morphology of V_1 and V_2 would correspond to the orientation of the precordial electrode to the left high septal mass, across necrotic tissue of the inferior portion of the septum and of the right ventricular septal mass. A left intraventricular tracing of the same case (Fig. 20) shows qRS morphology, and this favors a diagnosis of left bundle branch block with low septal involvement. The necropsy findings of the above case were the following: "Fibrosis of the inferior one-third of the septum and the free wall of the left ventricle. In addition there is a fibrotic zone 15 mm. in diameter in the anterosuperior region of the septum, which extends to the septal endocardium of the right ventricle, and in the other direction to within 3 mm. of the left septal endocardium."

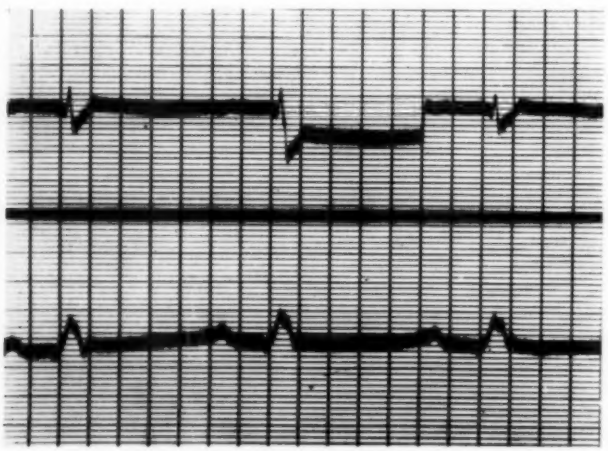

Fig. 20.—A left intraventricular tracing (first tracing), simultaneously with a precordial lead V_7 (second tracing), corresponding with the case of Fig. 19. The presence of a positive element in the intraventricular tracing supports the possibility of left bundle branch block.

C. *Septal Infarction Complicated by a Right Bundle Branch Block.*—

The rarity of right bundle branch block in the entire group of septal infarcts is notable.

A right bundle branch block with destruction of the inferior one-third of the septum, or more frequently of more extensive zones, but sparing a superior portion, determines the appearance of a Q wave in the right precordial leads and in the leads oriented toward the base of the interventricular septum (transitional zone).

The tracing in Fig. 21 shows right bundle branch block. The presence of qR complexes in V_1 and V_2, Qr in V_3, V_4 and W complexes in V_5, suggest the presence of an infarction of the inferior portion of the interventricular septum

and of the free wall of the left ventricle. The autopsy showed: ". . . the infarct extends into the septum in its anteroinferior two-thirds; it involves the full thickness of the septum to the right septal surface in its inferior one-third. In the remaining portions, there is a thin spared region in the right septal surface. The infarct involves the free wall of the left ventricle."

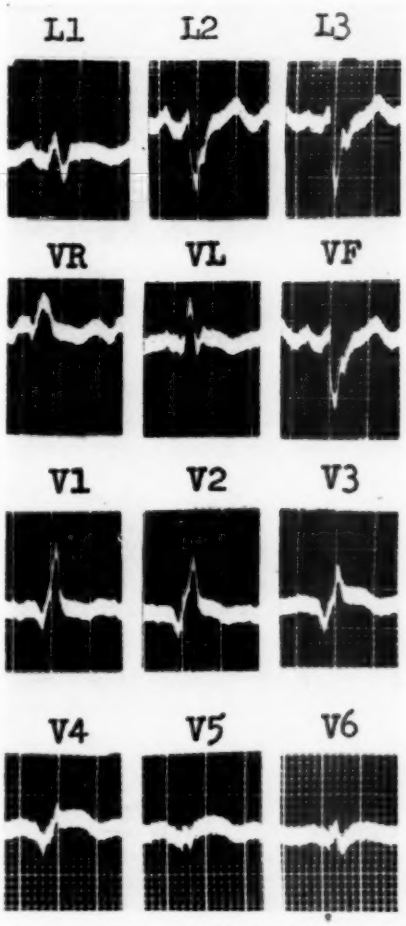

Fig. 21.—Demonstrates a right bundle branch block with QR complexes from V_1 to V_4 and qrs in V_5 and V_6. The autopsy showed an infarction of the anteroinferior two-thirds of the septum and the free wall of the left ventricle.

If the infarction extends to the anterior face of the right ventricle, theoretically we can expect a diminution or the disappearance of the late R of this phenomenon when the right septum is sufficiently involved. Even when the peripheral leads suggest a right bundle branch block, we can obtain essentially negative complexes in the right precordial leads.

D. *Infarctions of the Superior One-third of the Septum, Complicated With Bundle Branch Block.*—

In our series, we found only three cases with localization limited to the superior one-third of the septum; one of these had an infarction in the antero-

superior region, and the other two had posterosuperior localization. These two latter cases presented, in addition, involvement of the free wall of the right ventricle. We did not find electrocardiographic data in these cases which would enable us to suspect septal involvement. Even though there was an alteration of conduction in these three cases, two of them, with right bundle branch block, were in patients with rheumatic fever, and the other case, with left bundle branch block, presented hypertensive heart disease. It is possible that the alteration of conduction might have been the result of the primary illness and not due to the septal infarction.

The possibility of focal intraventricular blocks has not been analyzed in this paper, in view of the fact that the paucity of knowledge, at present, of this anomaly does not permit assigning to it a specific morphology of tracing.

III. FIBROSIS OF THE SEPTUM

In this group, we include thirteen cases in which the autopsy showed zones of fibrosis in the septum, the greater part of which were of genuine importance but which were not sufficiently confluent to constitute a true infarction. Seven of these patients presented alterations of intraventricular conduction which could be interpreted as left bundle branch block in six cases and right bundle branch block in one. Of the cases with left bundle branch block, two were aortic stenosis, one syphilitic aortitis, one was cardio-angiosclerosis, and the other was a case of arterial hypertension. The case with right bundle branch block was in a patient with rheumatic endomyocarditis. It is very probable that in some of these cases the fibrotic lesions in the septum constituted a determining factor in the conduction abnormality, but we are not able to state this definitely because of the lack of histologic study of the branches of the His bundle in these cases. On the other hand, in none of these cases did we find electrocardiographic additional data which would enable us to suspect septal damage.

SUMMARY

We have analyzed the principal electrocardiographic signs that permit the diagnosis of a necrotic zone in the interventricular septum and have applied this analysis to the cases of septal infarction found in the autopsy files of the Instituto Nacional de Cardiología.

Corresponding to the extent of the septal damage found in the autopsy, the cases were studied in the following manner:

1. Massive infarctions of the septum. Where there is no bundle branch block, the electrocardiographic pattern is characterized by the presence of QS complexes in the precordial leads oriented toward the interventricular septum (V_3, V_4; or perhaps from V_1 to V_4). Frequently, this type of infarction is complicated by a complete or incomplete left bundle branch block, and in these conditions the diagnosis is possible because of the presence of a Q wave in leads oriented toward the lateral face of the left ventricle, and, above all, by the presence of QrS complexes in transitional zones (V_3, V_4).

In case of right bundle branch block, important destruction of the septum is responsible for the appearance of Q waves in the right precordial leads or in transitional zones.

2. Infarctions of the inferior one-third of the septum.

In this group we have noted a high incidence of complete or incomplete left bundle branch block.

When there is no bundle branch block, the diagnosis can be very difficult. The presence of QS complexes from V_1 to V_4 or in V_3, V_4, permits a diagnosis of septal damage, although it is practically impossible to differentiate this picture from that of massive infarction.

If the infarction of the inferior one-third of the septum is complicated by a left bundle branch block, the diagnosis is made by the presence of qRs complexes in V_3 and V_4 and by the Q wave in the leads oriented to the free wall of the left ventricle.

When this type of infarction is complicated by a right bundle branch block, a Q wave is seen in the right precordial leads and its magnitude is accentuated in direct proportion to the extent of septal damage.

In those cases in which the infarction extends into the free wall of the right ventricle, it is possible to trace, in the right precordial leads, the morphology found in the high portions of the septum.* In cases of left bundle branch block, the morphology may simulate right side alterations of conduction.

3. Infarctions of the superior third of the septum.

In all of the cases, there was bundle branch block; nevertheless, electrocardiographic data which would suggest septal damage was not seen.

4. Fibrosis of the septum.

Even when on occasion the fibrous zones scattered in the septum were of considerable extent, we did not find an electrocardiographic tracing characteristic of this condition. In some cases, there was a left bundle branch block which may or may not have been the result of the fibrotic zones.

REFERENCES

1. Levy, L., and Hymann, A. L.: Difficulties in the Electrocardiographic Diagnosis of Myocardial Infarction, Am. Heart J. **39:**243, 1950.
2. Roesler, H., and Dressler, W.: An Electrocardiographic Pattern of Infarction of the Interventricular Septum Extending From the Anterior to the Posterior Aspects of the Heart, Am. Heart J. **34:**817, 1947.
3. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries. *In* Levy, Robert: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company.
4. Wilson, F. N.: Form of the Electrocardiogram. Diagnosis and Treatment of Cardiovascular Diseases, Stroud, W. D., Philadelphia, 1943, F. A. Davis Company.
5. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, 1946, Lea & Febiger.
6. Rosenbaum, F. F., Wilson, F. N., and Johnston, F. D.: Changes in the Precordial Electrocardiogram Produced by Extension of Anteroseptal Myocardial Infarction, Am. Heart J. **30:**11, 1945.
7. Myers, G. B., Klein, H. A., and Stofer, B. E.: Correlation of Electrocardiographic and Pathologic Findings in Anteroseptal Infarction, Am. Heart J. **36:**535, 1948.
8. Sodi-Pallares, Demetrio.: Nuevas Bases de la Electrocardiografia, Ed. Inst. Cardiología México, 1951.
9. Lepeschkin, E.: Modern Electrocardiography, Baltimore, 1951, Williams & Wilkins Company.
10. Wilson, F. N., Hill, I. G., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction, Am. Heart J. **9:**956, 1936.

11. Dressler, W., Roesler, H., and Schwager, A.: The Electrocardiographic Signs of Myocardial Infarction in the Presence of Bundle Branch Block. I. Myocardial Infarction With Left Bundle Branch Block, Am. Heart J. **39**:217, 1950.
12. Dressler, W., Roesler, H., and Schwager, A.: The Electrocardiographic Signs of Myocardial Infarction in the Presence of Bundle Branch Block. II. Myocardial Infaction With Right Bundle Branch Block, Am. Heart J. **39**:545, 1950.
13. Sodi-Pallares, D., Rodríguez, M. I., Chait, L. O., and Zuckermann, R.: The Activation of the Interventricular Septum, Am. Heart J. **41**:569, 1951.
14. Sodi-Pallares, D., and Rodríguez, M. I.: Morphology of the Unipolar Leads Recorded at the Septal Surfaces. Its Application to the Diagnosis of Left Bundle Branch Block Complicated by Myocardial Infarction, Am. Heart J. **43**:27, 1952.
15. Sodi-Pallares, D., Rodríguez, M. I., and Bisteni, A.: Diagnóstico electrocardiográfico del bloqueo de rama izquierda complicado con infarto del miocardio, Arch. Inst. cardiol. México **22**:1, 1952.
16. Sodi-Pallares, D., Vizcaíno, M., Soberón, J., and Cabrera, E.: Comparative Study of the Intracavitary Potential in Man and Dog, Am. Heart J. **33**:819, 1947. Arch. Inst. cardiol. México **17**:630, 1947.
17. Sodi-Pallares, D., Estandía, A., Soberón, J., and Rodríguez, M. I.: The Left Intraventricular Potential of the Human Heart. II. Criteria for Diagnosis of Incomplete Bundle Branch Block, Am. Heart J. **40**:655, 1950.
18. Sodi-Pallares, D., Bisteni, A., and Hermann, G.: Some Views on the Significance of qR and QR Type Complexes in Right Precordial Leads in the Absence of Myocardial Infarction, Am. Heart J. **43**:716, 1952.
19. Master, A. M., Dack, S., and Jaffe, H. L.: Bundle Branch and Intraventricular Block in Acute Coronary Occlusion, Am. Heart J. **39**:217, 1950.
20. Comeau, W. J., Hamilton, J. G. M., and White, P. D.: Paroxysmal Bundle Branch Block Associated With Heart Disease, Am. Heart J. **15**:276, 1938.
21. Rodríguez, M. I., and Sodi-Pallares, D.: The Mechanism of Complete and Incomplete Bundle Branch Block, Am. Heart J. **44**:715, 1952.

THE DIAGNOSIS OF MYOCARDIAL INFARCTION IN PATIENTS WITH ANOMALOUS ATRIOVENTRICULAR EXCITATION (WOLFF-PARKINSON-WHITE SYNDROME)

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THE ELECTROCARDIOGRAPHIC diagnosis of myocardial infarction in patients with anomalous atrioventricular excitation (Wolff-Parkinson-White Syndrome) is beset with many difficulties. Although the short P-R interval and abnormal QRS complex are sufficiently characteristic to be diagnostic in most cases, the syndrome is still commonly overlooked.[1] The anomalous component, which initiates the QRS group of deflections, may be mistaken for part of a diphasic or notched P wave, and the succeeding sharp downward deflection for a Q wave, leading to the false notion that the patient is suffering from myocardial infarction.[2] On the other hand, variations in the contour of the ventricular complex may occur spontaneously, presumably due to the presence of multiple anomalous pathways,[3,4] and these may be mistaken for changes which indicate infarction.

A third source of error is the diagnosis of myocardial infarction solely on the basis of S-T segment and T wave changes in electrocardiograms which display anomalous conduction. Since such changes, in the absence of specific QRS signs, at most may be said to represent sublethal injury, the diagnosis of infarction under these circumstances is open to question. Abnormalities of the T wave and S-T segment are part of the characteristic pattern of infarction, but they also occur in many other conditions, such as pericarditis, myocarditis, pulmonary embolism, tachycardia, electrolyte imbalance, febrile reactions, cardiac hypertrophy, intraventricular block, under neurogenic influences, and following the use of certain drugs. Moreover, these changes may occur as the result of anomalous conduction itself. These considerations are fundamental and are pertinent whether the order of ventricular excitation is normal or abnormal. Caution in interpretation is all the more desirable in the type of case under consideration, since we shall show that the anomalous order of ventricular excitation precludes the development of QRS signs which are diagnostic of infarction.

There is considerable evidence that the T waves and S-T segments are unstable in the presence of anomalous conduction.[5-9] Marked variability of the T waves was a striking feature in the case reported by Eichert[5] in 1944, and led to

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considerable diagnostic confusion. Wendkos and Nadler[8] concluded that this instability is similar to that which occurs in neurocirculatory asthenia, and that heightened adrenergic activity is a characteristic feature of the Wolff-Parkinson-White Syndrome. They were able to provoke bizarre terminal ventricular deflections by augmentation of sympathetic activity (vertical stance or amyl nitrite).

Rapid heart action itself must be thought of as a possible cause of T wave and S-T segment aberration, since paroxysmal tachycardia occurs in 70 per cent of the patients in this group.[1]

Finally, the tracings published by Tamagua and associates[10] reveal that striking T-wave changes can be produced simply by varying the degree of pre-excitation.

It would seem, then, that a diagnosis of myocardial infarction based on abnormalities of the T wave and S-T segment alone, especially in electrocardiograms displaying anomalous excitation, is unwarranted. Yet, with few exceptions,[7,11,12] the fact that anomalous conduction masks the electrocardiographic signs of myocardial infarction appears to have been overlooked. Although normally conducted beats appeared spontaneously in one-half of the ten reported cases of anomalous conduction presumably complicated by myocardial infarction,[11-15] their importance for the diagnosis of this lesion was rarely mentioned.[11,12] Autopsy confirmation of infarction was obtained in one of these cases, and it is noteworthy that electrocardiographic signs of the lesion were displayed by the normally conducted beats, but not by the anomalous ones.[13] In the other cases[6,7,16-18] normally conducted beats did not occur, and no attempt to induce them was made.

The importance of observing normally conducted beats in patients with the Wolff-Parkinson-White Syndrome when myocardial infarction is suspected cannot be overemphasized. Since such complexes occur spontaneously in about one-half of the cases,[1,2,6,7,11,13-18] the simple expedient of obtaining frequent electrocardiograms may provide the desired diagnostic material. If normal beats do not occur spontaneously, every effort should be made to induce their appearance. Our recent experience in patients with anomalous conduction suggests that this can be accomplished in most cases. Within the past year we have studied four cases of myocardial infarction and anomalous atrioventricular excitation, and these form the basis of the present report.

CASE REPORTS

CASE 1.—M. M. (Beth Israel Hospital, # M-28722), a 50-year-old man, was admitted for the first time on July 12, 1948, four days following an attack of severe crushing precordial pain radiating to the shoulders and both arms, necessitating repeated hypodermic injections for relief. Burning precordial pain and a sticking substernal sensation had been noted on effort, for several months prior to admission.

Examination disclosed a pulse rate of 90, blood pressure 120/55 mm. Hg, crepitant râles at the right lung base, an apical systolic murmur, and a questionable transient pericardial friction rub.

The only noteworthy laboratory findings were a corrected sedimentation rate of 2.0 mm. per minute, and enlargement of the heart on roentgenogram examination. The electrocardiograms will be described below.

Except for several attacks of chest pain, the clinical course was uneventful, and he was discharged improved on Aug. 11, 1948.

Second Admission: March 12, 1952: His health had been good except for rectal bleeding. The blood pressure was 160/100 mm. Hg, but the findings were not remarkable otherwise. Hemorrhoidectomy was done on March 17 under spinal anesthesia. He was discharged improved on March 22, 1952.

Electrocardiographic observations: First admission.—The tracings displayed both anomalous and normal atrioventricular excitation. Signs of anterior myocardial infarction were consistently revealed in the normally conducted beats, but were never evident in the anomalous complexes (Fig. 1). Mechanical stimulation of either right or left carotid sinus, when normal conduction was present, induced either aberrant beats, or atrioventricular nodal rhythm without change in the morphology of QRS-T (Fig. 2).

The patient came to the laboratory by request on Nov. 10, 1951. Electrocardiograms and vectorcardiograms disclosed normal atrioventricular conduction and healed anterior myocardial infarction. Repeated right or left carotid sinus stimulation failed to change the outline of the ventricular complexes.

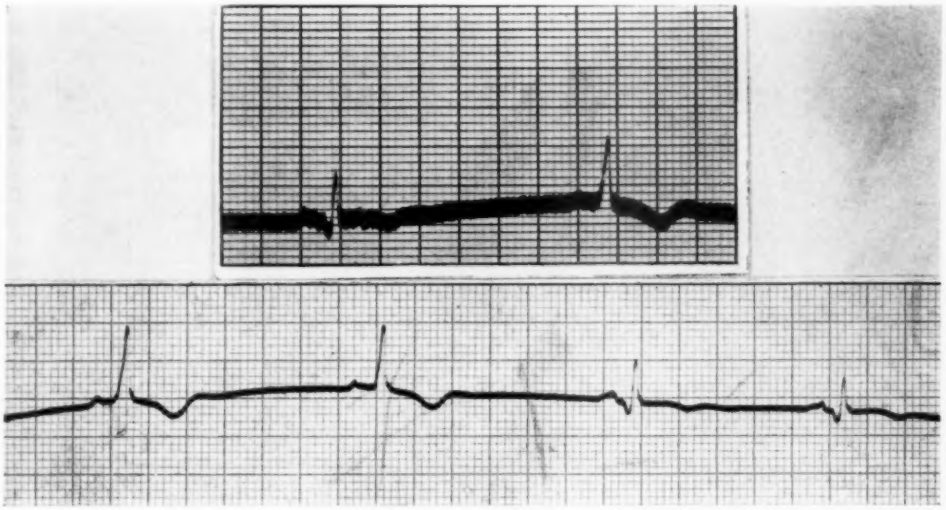

Fig. 1 (Case 1).—Top row: Normal P-R and QRS intervals replaced by unusually short P-R and abnormally long QRS intervals coincident with carotid sinus stimulation. Bottom row: Return to normal P-R and QRS intervals upon discontinuance of carotid sinus stimulation.

Same as Fig. 109, p. 180, *Electrocardiography: Fundamentals and Clinical Application*, by Louis Wolff, M. D., W. B. Saunders Company, Reproduced by courtesy of the Publishers.

Second Admission: March 18, 1952: Electrocardiographic observation over a prolonged period of time and repeated stimulation of the carotid sinus revealed normal conduction consistently. At the conclusion of the period of observation the patient was given 0.8 mg. digitoxin orally.

March 19, 1952: An additional dose of 0.4 mg. digitoxin was given at 7:00 A.M., and three and one-half hours later (twenty hours after the first dose); anomalous atrioventricular excitation was present almost exclusively. The incidence of the normal beats gradually increased, however, and by 11:15 A.M. they had almost completely replaced the aberrant ones. At this time abnormal beats could be induced easily by gentle massage of either carotid sinus. The abnormal rhythm, having appeared, persisted for varying intervals before spontaneously reverting to the normal type, or conversion could be promptly induced by inspiration (Fig. 3*A*). This mechanism was so sensitive, that the abnormal rhythm could be maintained for a prolonged period only by the patient holding his breath (Fig. 3, *B*, *C*).

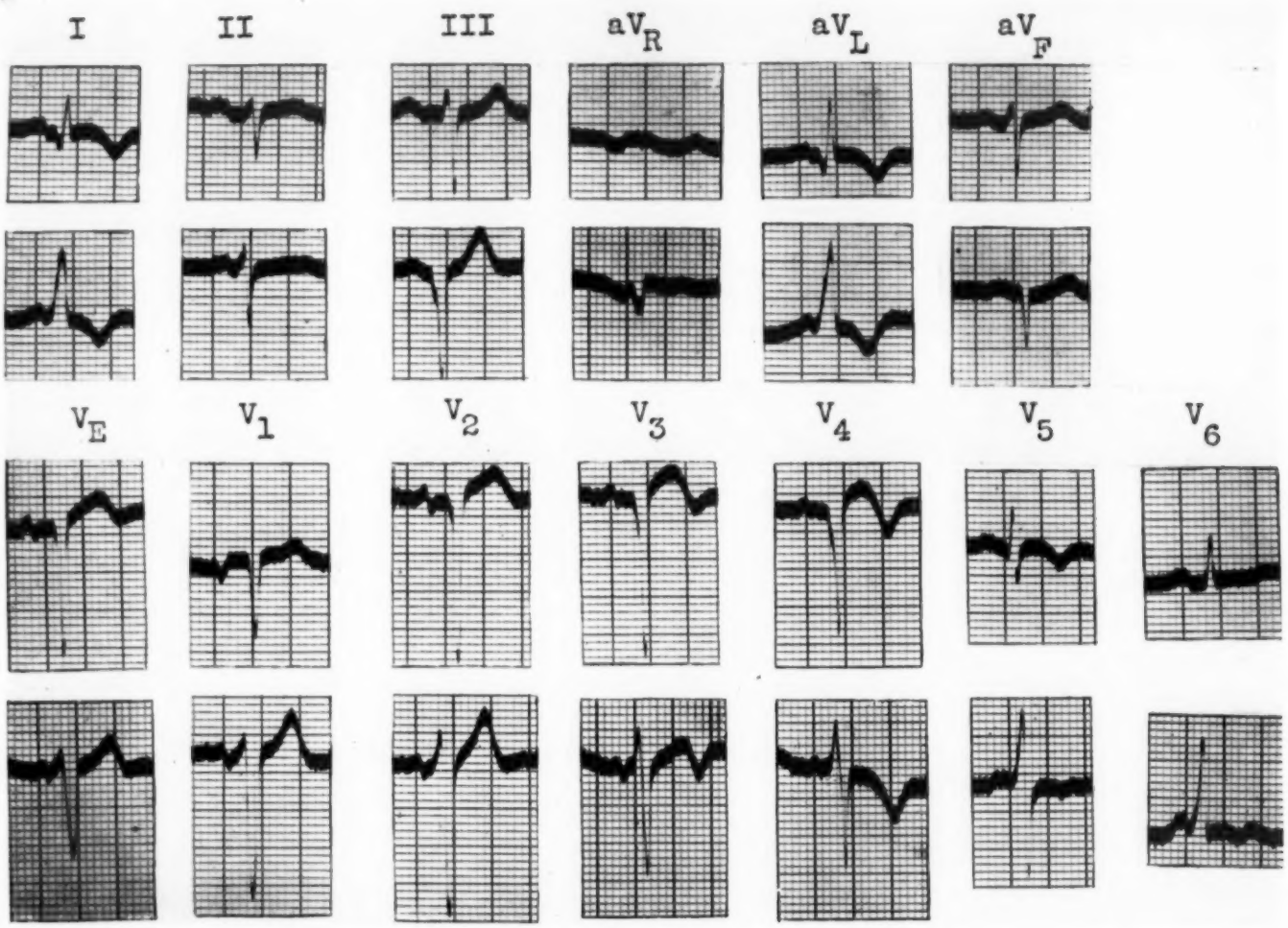

Fig. 2 (Case 1).—Limb and precordial leads from same case as Fig. 1 during normal atrioventricular conduction and anomalous atrioventricular conduction. Top and third rows: Limb and precordial leads during normal atrioventricular conduction. Second and bottom rows: Limb and precordial leads during anomalous atrioventricular conduction. Signs of anterior infarction present with normal conduction, absent with anomalous conduction. Same as Fig. 110, p. 181, *Electrocardiography: Fundamentals and Clinical Application*, by Louis Wolff, M. D., W. B. Saunders Company. Reproduced by courtesy of the publishers.

atrioventricular conduction. Top and third rows: Limb and precordial leads during normal atrioventricular conduction. Second and bottom rows: Limb and precordial leads during anomalous atrioventricular conduction. Signs of anterior infarction present with normal conduction, absent with anomalous conduction. Same as Fig. 110, p. 181, *Electrocardiography: Fundamentals and Clinical Application*, by Louis Wolff, M. D., W. B. Saunders Company. Reproduced by courtesy of the publishers.

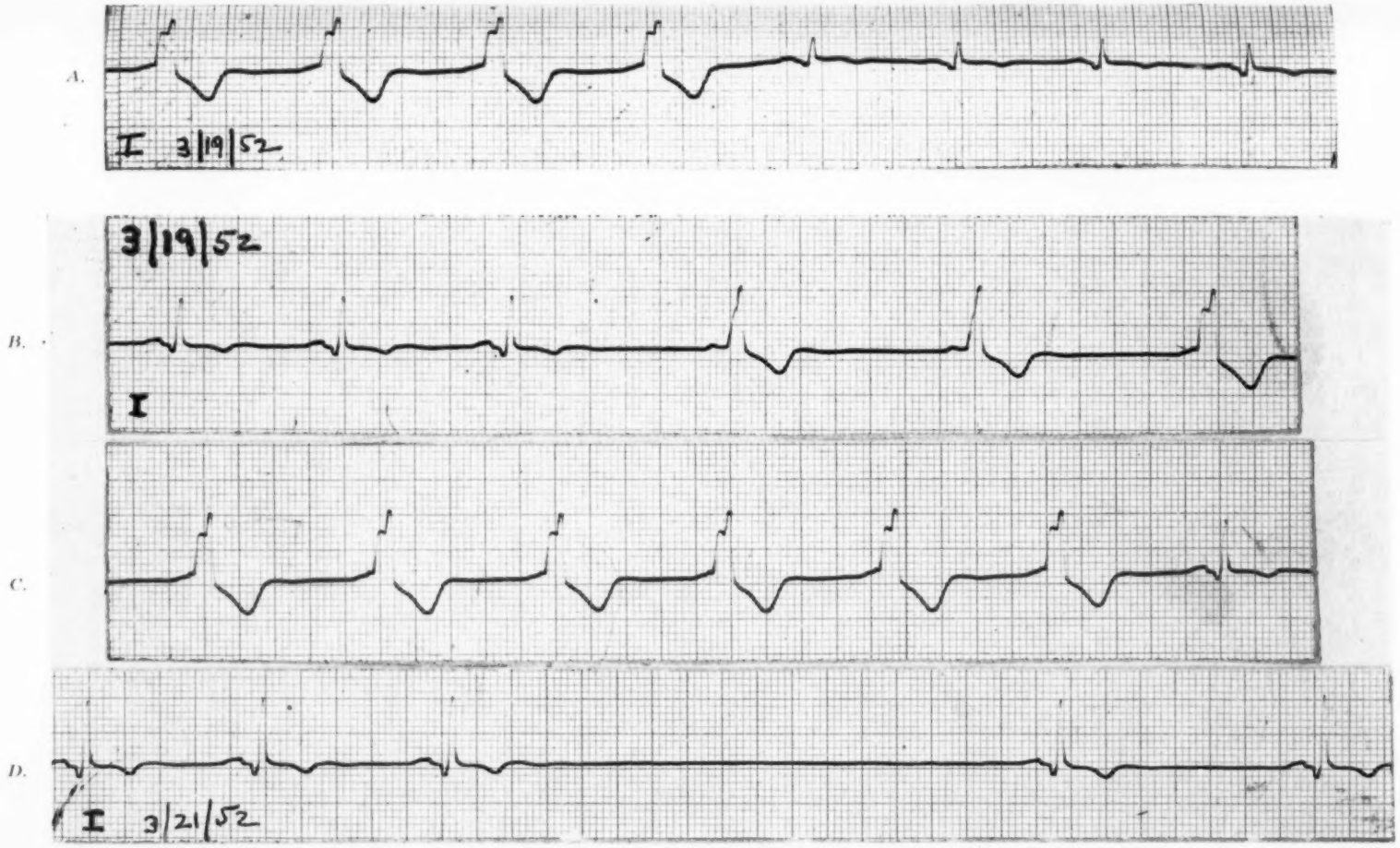

Fig. 3 (Case 1).—*A*, Digitalization completed. Interruption of anomalous conduction coincident with a deep inspiration. See text.

Fig. 3 (Case 1).—*B*, and *C*, Same day as Fig. 3*A*. Continuous Lead I. Anomalous rhythm appears during stimulation of the carotid sinus, and persists as long as the patient holds his breath.

Fig. 3 (Case 1).—*D*, Two days after discontinuation of digitalis. Lead I. Anomalous conduction is not induced, despite asystole lasting 3.4 seconds as the result of carotid sinus stimulation.

March 21, 1952: Only normal complexes were noted, despite repeated carotid sinus stimulation (Fig. 3*D*), forced respiration, and the Valsalva experiment. An additional and final dose of 0.4 mg. digitoxin was administered. Four hours later anomalous complexes again predominated, but reversion to normal rhythm was easily effected by deep inspiration.

An electrocardiogram obtained on Aug. 13, 1952 displayed normal conduction.

CASE 2.—W. M. (Beth Israel Hospital, # M-29707), a 79-year-old man, was admitted for the first time on Jan. 21, 1952, one day following the occurrence of severe prolonged chest pain. There was a past history of hypertension, and intermittent chest pain of brief duration. On admission he appeared critically ill, the temperature and white cell count were elevated, and the blood pressure was 127/70 mm. Hg. A transient pericardial friction rub and short paroxysms of auricular fibrillation were noted on the third hospital day. Signs of congestive failure appeared, and he was digitalized. After a stormy course he improved and was discharged on the twenty-sixth hospital day with instructions to take 0.2 mg. digitoxin daily. He was followed in the cardiac clinic.

He did well on restricted activity. The digitoxin was discontinued on March 29, 1952, but was resumed on May 2, 1952. On April 11, 1952, he had slight precordial pressure without radiation, lasting twenty minutes. One week later, after walking up two flights of stairs, he experienced severe substernal pressure of twenty minutes duration. The following morning, April 19, 1952, persistent substernal pressure was provoked by a walk of several blocks, and he was readmitted to the hospital.

Second Admission: The patient appeared critically ill. The skin was ashen, cold, and moist, the blood pressure was 106/70 mm. Hg, and bilateral basal crepitant râles were noted. The heart sounds were of poor quality, and there was a harsh apical systolic murmur. Recurrent pain and dyspnea characterized the clinical course, and on May 7, 1952, pulmonary edema and vascular collapse occurred. His condition gradually deteriorated, and he expired on May 24, 1952. Autopsy revealed extensive anterior and posterior myocardial infarction.

Electrocardiographic Observations: Many experiments were performed, and the results are shown in Table I and Figs. 4 to 10. Constant observation of the cardiac mechanism for the duration of the experiments in this and other patients was accomplished either by continuous recording of electrocardiograms or the inspection of the fluorescent screen of the oscilloscope used in obtaining vectorcardiograms. The electrocardiograms are described in detail in the text and in the legends.

Anomalous atrioventricular excitation was at first intermittently, then constantly, present, except on April 30, 1952, thirty-two days after digitalis was omitted (Table I). Subsequent to redigitalization on May 2, 1952, all tracings again disclosed anomalous conduction (Fig. 10). However, conversion of the cardiac mechanism could be effected repeatedly (Table I), and then right bundle branch block was invariably present, as it was when conversion occurred spontaneously. The signs of anterior and posterior myocardial infarction were always clearly revealed in the presence of right bundle branch block, but absent when conduction was anomalous (Fig. 4).

CASE 3.—E. G. (Beth Israel Hospital, # M-29540), a 55-year-old woman, was admitted on April 13, 1952. There was a one to two year history of exertional chest pain and dyspnea, two to three pillow orthopnea, and hypertension. Six attacks of severe chest pain radiating to the shoulder, and lasting about fifteen minutes, occurred in the five days preceding hospitalization.

Examination disclosed a very obese woman, pulse rate 88, blood pressure 210/130 mm. Hg, cardiomegaly, and a moderately loud apical systolic murmur.

The corrected sedimentation rate on admission was 19 mm. in one hour, but one week later was 31; the final determination, three weeks after entry, was 39. Other laboratory findings, except for the electrocardiograms, were not remarkable.

The patient was treated with anticoagulants, and following an uneventful course, was discharged improved on May 9, 1952.

Electrocardiographic Observations: One of the tracings obtained on the first hospital day was essentially normal, and since all the other electrocardiograms disclosed anomalous conduction, electrocardiographic confirmation of the clinical diagnosis of myocardial infarction was lacking.

Fig. 4.

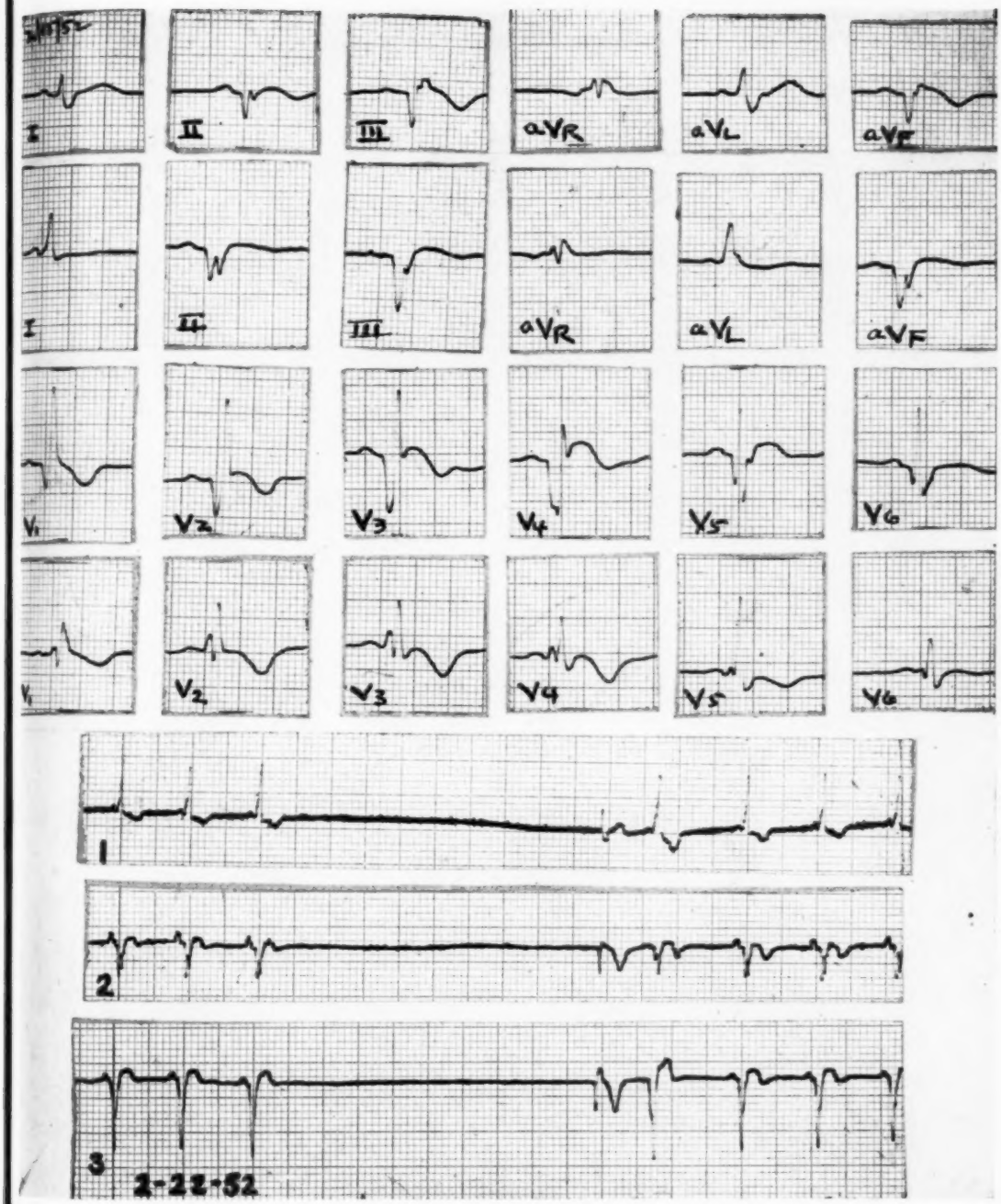

Fig. 5.

Fig. 4 (Case 2).—Limb and precordial leads during normal atrioventricular conduction and anomalous atrioventricular conduction. Top and third rows: limb and precordial leads during right bundle branch block. Second and bottom rows: limb and precordial leads during anomalous atrioventricular conduction. Signs of anterior and posterior infarction present with normal (see footnote to summary) conduction, absent with anomalous conduction. Note the QS deflections in Leads II, III, and aV_F (second row), and masking of abnormal S-T segment displacement by anomalous excitation (bottom row).

Fig. 5 (Case 2).—Leads I, II and III recorded simultaneously at a camera speed of 10 mm. per second. Asystole for 2.9 seconds follows right carotid sinus stimulation. On resumption of cardiac activity the first beat is atrioventricular nodal, the second one an auricular premature beat. The atrioventricular nodal beat displays right bundle branch block, the premature beat modified anomalous conduction, and the remaining complexes anomalous conduction. Only the atrioventricular nodal beat displays the signs of posterior infarction.

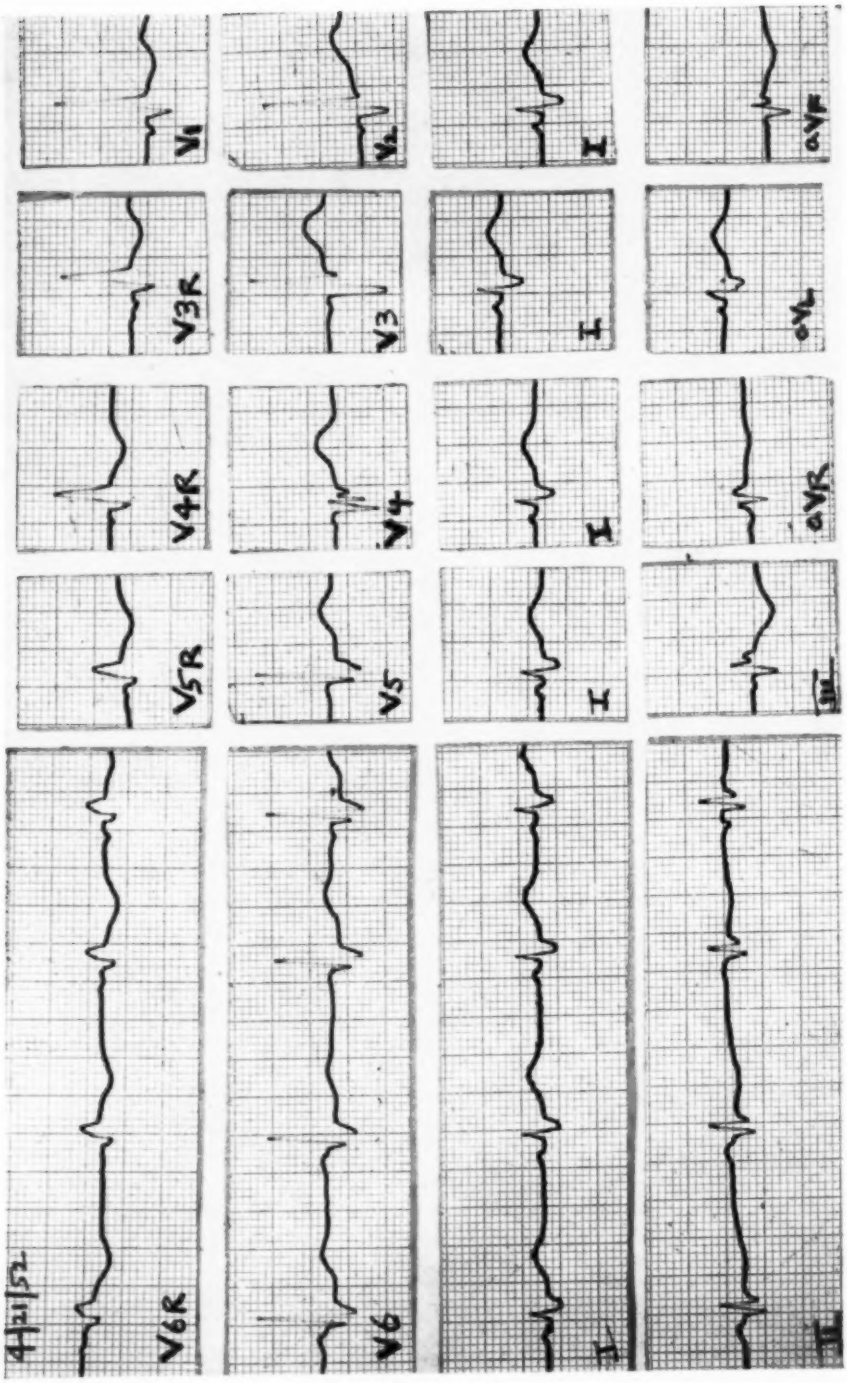

Fig. 6 (Case 2).—Leads I, II, V_6, and V_{6R} recorded simultaneously (strips containing four complexes), and the remaining leads recorded simultaneously with Lead I. Right bundle branch block appeared one hour and twenty-five minutes after a single dose of 0.6 Gm. quinidine. The long strips show the spontaneous development of atrioventricular nodal rhythm, which is also present in the single complexes (note the P waves in Leads II, III, and aV_R).

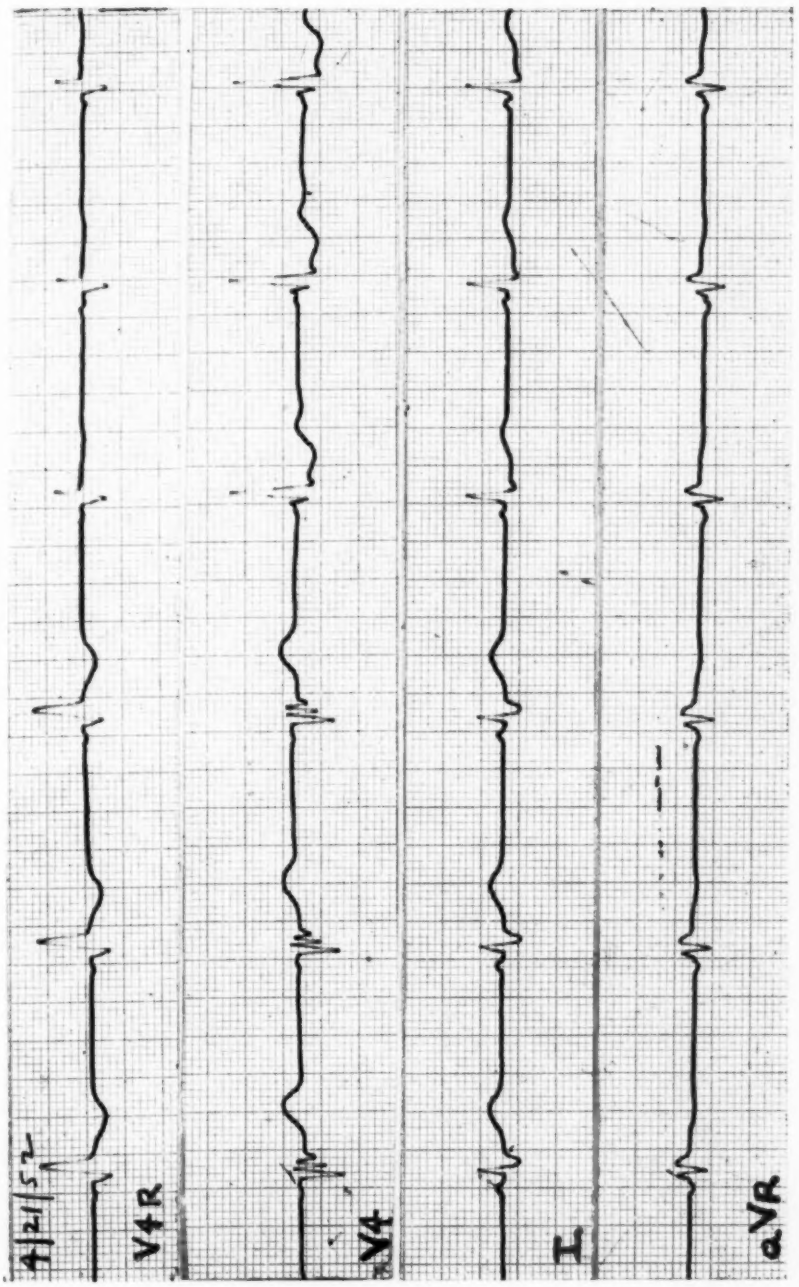

Fig. 7 (Continuation of Fig. 6).—Simultaneous Leads V_{4R}, V_4, I, and aV_R. Conversion to sinoauricular rhythm and anomalous conduction by carotid sinus stimulation. These changes are best seen in Lead V_4.

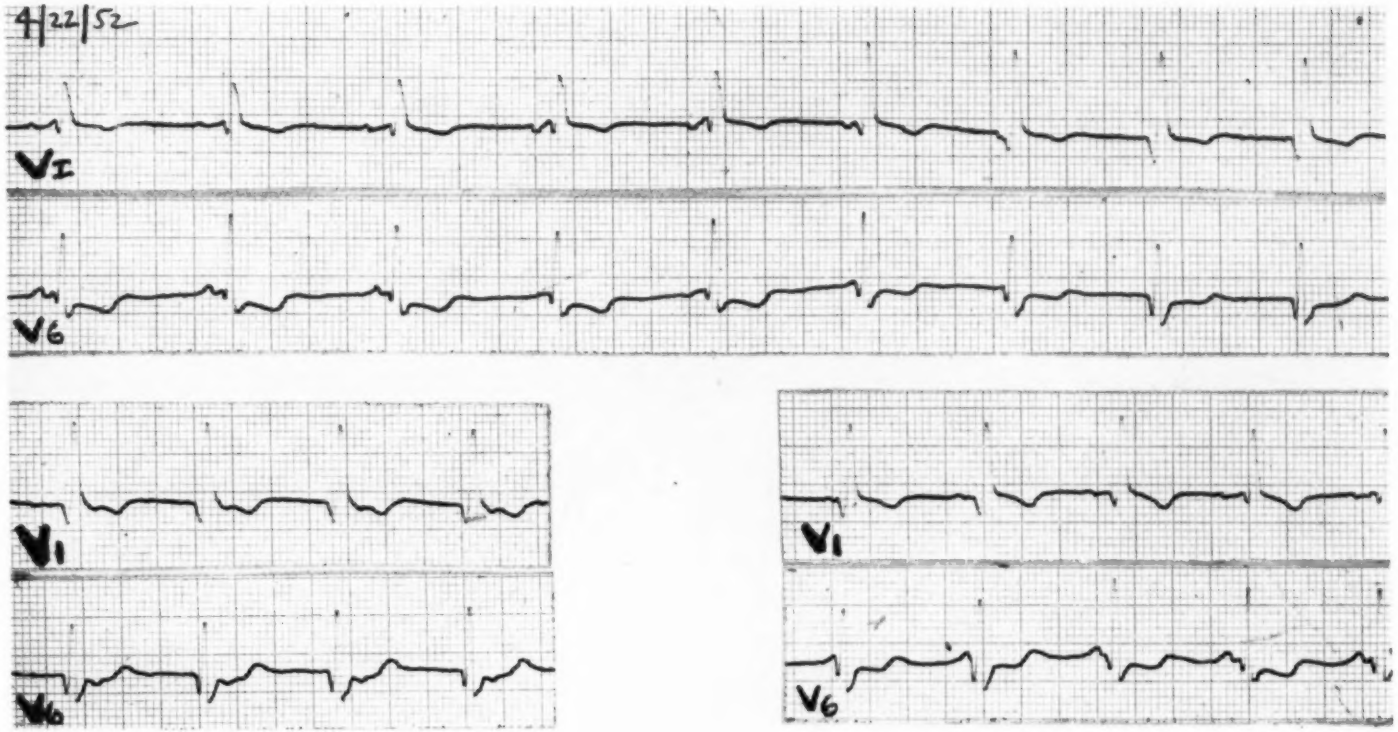

Fig. 8 (Case 2).—Continuous simultaneous Leads V_1 and V_6. Thirty seconds after the intravenous injection of 0.9 mg. atropine anomalous conduction is replaced by right bundle branch block, coincident with the establishment of atrioventricular nodal rhythm. The P-R interval becomes progressively shorter, and the P waves disappear before finally emerging as inverted deflections following the QRS group. During this interval the ventricular complexes change gradually, probably due to the progressive displacement of the pacemaker from the upper reaches to the lower reaches of the atrioventricular node. In the first part of the lower two strips both auricles and ventricles respond to impulses arising low in the atrioventricular node; the curves are those of right bundle branch block, and they display the signs of infarct. In the second part of the lower strips sinoauricular rhythm and anomalous conduction are re-established, and the signs of infarct disappear.

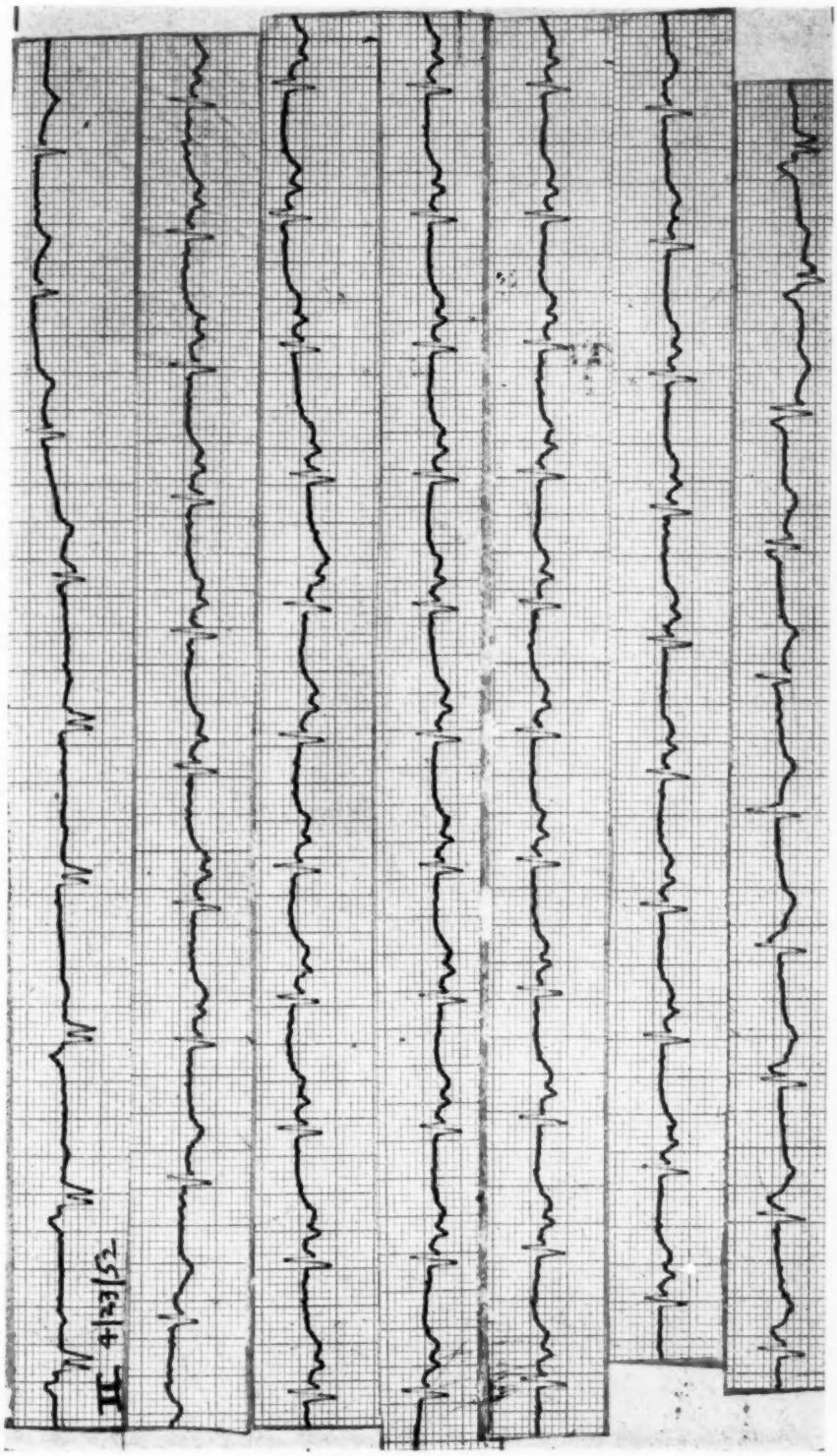

Fig. 9 (Case 2).—Continuous Lead II. Atrioventricular nodal rhythm and right bundle branch block appear 45 seconds after the intravenous injection of 0.9 mg. atropine, and last 48 seconds. See text.

TABLE I. EFFECT OF VARIOUS MEASURES ON ANOMALOUS CONDUCTION. CASE 2

DATE	CONTROL ELECTRO-CARDIOGRAM	PROCEDURE	EFFECT
2/12/52	Anomalous	Carotid sinus stimulation	Slowing
2/13/52	Anomalous	0.4 Gm. quinidine Carotid stimulation	None Slowing
2/15/52	Anomalous	0.6 Gm. quinidine at 9:45 A. M.	Right bundle branch block at 11:30 A. M.
		Right carotid stimulation	Anomalous conduction
		0.3 Gm. quinidine at 11:45 A. M.	Right bundle branch block at 1:15 P. M.
		Right carotid stimulation at 2:15 P. M.	Anomalous conduction
2/22/52	Anomalous	Right carotid stimulation	A single A-V nodal beat with right bundle branch block, ending a period of asystole of 2.9 seconds
		0.6 Gm. quinidine at 10:50 A. M.	No change 2 hours later, anomalous conduction persisting
2/28/52	Anomalous	0.6 Gm. quinidine at 1:35 P. M.	No change at 2:40 P. M.
		0.3 Gm. quinidine at 2:40 P. M.	No change at 4:58 P. M.
		0.9 mg. atropine subcutaneously at 4:58 P. M.	No change in 20 minutes
3/29/52	Anomalous	0.9 Gm. quinidine at 9:30 A. M.	No change at 11:50 A. M.
		0.3 Gm. quinidine at 11:50 A. M.	Right bundle branch block at 1:15 P. M.
		Right carotid stimulation at 1:35 P. M.	Marked sinus slowing
		Right carotid stimulation at 2:40 P. M.	Marked slowing. No change at 2:50 P. M., right bundle branch block still being present
		Digitalis omitted	

Attempts to convert the cardiac mechanism were made on nine different days, and the results are summarized in Table II. Only one of the procedures tried was successful in establishing normal intraventricular conduction, namely amyl nitrite* inhalation two to four hours following the oral administration of quinidine; it was repeatedly effective (Table II). The normally conducted beats reveal the presence of posterior myocardial infarction, which is completely masked in the anomalous complexes (Fig. 11).

*This drug, or other potent vasodilators, should not be administered during the early stage of myocardial infarction.

TABLE I. (CON'T)

DATE	CONTROL ELECTRO-CARDIOGRAM	PROCEDURE	EFFECT
4/ 5/52	Anomalous	0.6 Gm. quinidine at 10:25 A. M.	No change at 1:10 P. M.
4/12/52	Anomalous	0.6 Gm. quinidine	No change
4/19/52	Anomalous		
4/20/52	Anomalous		
4/21/52	Anomalous	0.6 Gm. quinidine at 11:50 A. M.	Right bundle branch block at 1:15 P. M. Occasional A-V nodal beats, then persistent A-V nodal rhythm
		Carotid stimulation	Sinoauricular rhythm and anomalous conduction
4/22/52	Anomalous	0.9 mg. atropine intravenously at 12:52 P. M.	A-V nodal rhythm and right bundle branch block 30 seconds later
4/23/52	Anomalous	0.9 mg. atropine intravenously	A-V nodal rhythm and right bundle branch block 45 seconds later, and lasting 48 seconds
4/24/52	Anomalous	1.0 mg. atropine subcutaneously at 11:25 A. M.	No change, same rate
		Amyl nitrite inhalation at 12:40 P. M.	No change. Observations ended at 12:55 P. M.
4/28/52	Anomalous	2.0 mg. atropine subcutaneously at 3:35 P. M.	Rate change
		Amyl nitrite at 4:35 P. M.	No change. Observations ended at 4:40 P. M.
4/30/52	Right bundle branch block	Right and left carotid sinus stimulation	Slowing
5/ 2/52		Digitalized	
5/ 5/52	Anomalous		
5/ 6/52	Anomalous		
5/13/52	Anomalous		
5/20/52	Anomalous		

CASE 4.—S.H., a 69-year-old man, was seen by one of us (L. W.) on April 12, 1949. He had been hospitalized elsewhere three months previously, following sudden loss of consciousness while at work as a sheet metal worker; a diagnosis of myocardial infarction was made at that time. He had numerous complaints, including occasional nocturnal attacks of pressure in the upper chest, radiating to the jaw, and lasting one-half hour. Exertional dyspnea was troublesome, and he was taking digitalis regularly. There was a long history of hypertension.

Examination revealed absolute irregularity of the heart action, and of the radial pulse, at a rate of 68, blood pressure 240/130 mm. Hg, marked cardiomegaly, an apical systolic murmur, and signs of congestive failure.

He was examined again on June 15, 1949, May 15, 1950, and on June 18, 1952, when he was requested to come to the laboratory for vectorcardiographic study.

Electrocardiographic Observations: Tracings obtained on April 12, 1949, June 15, 1949, May 15, 1950, and June 18, 1952 were interpreted as auricular fibrillation, left bundle branch block, and rare complexes showing right bundle branch block. When vectorcardiograms were obtained the interpretation was changed from left bundle branch block to anomalous atrioventricular excitation. Occasional loops were characteristic of right bundle branch block. Electrocardiograms displaying both types of conduction are shown in Figs. 12 and 13. Anteroseptal and posterior myocardial infarction is revealed in the right bundle branch block curves, but not in the anomalous beats. The characteristic, heavily slurred, premature component of the anomalous beats is clearly evident, and QS deflections occur in Leads II, III, and aV_F. The small initial negative deflections in V_{4-6} are not constant, and are probably the result of fibrillation oscillations. The ventricular rhythm on June 20, 1952 was regular, but the ventricular complexes were similar to those obtained on previous occasions.

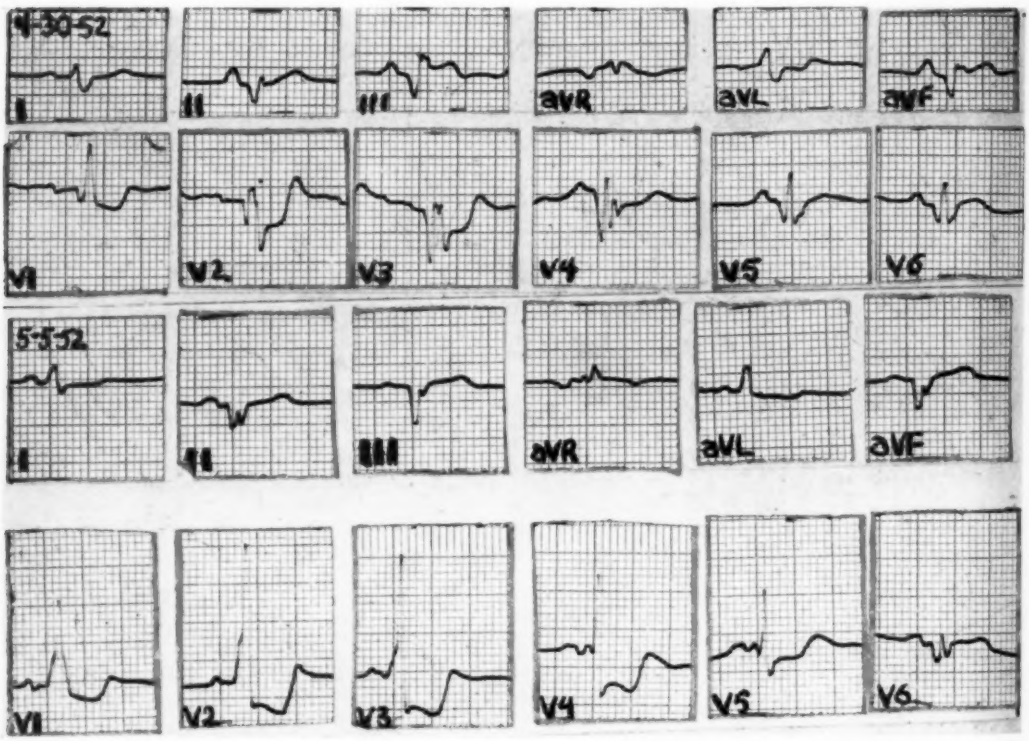

Fig. 10 (Case 2).—Limb and precordial leads during normal atrioventricular conduction and anomalous atrioventricular conduction. Top two rows: limb and precordial leads during right bundle branch block. Bottom two rows: limb and precordial leads during anomalous conduction. Signs of posterior and anterior infarction present with right bundle branch block and absent with anomalous conduction. See text.

PITFALLS IN THE INTERPRETATION OF ELECTROCARDIOGRAMS IN CASES OF THE WOLFF-PARKINSON-WHITE SYNDROME

Anomalous conduction not infrequently persists during paroxysms of tachycardia in patients with the Wolff-Parkinson-White Syndrome. Many observers

have attributed these paroxysms to an ectopic ventricular focus, presumably because of the aberrant complexes. Since we have recently reviewed the pertinent literature[1] the subject will not be discussed here. New observations, to be reported elsewhere, have confirmed our previous opinion that paroxysmal ventricular tachycardia does not occur in uncomplicated cases of this syndrome. This incorrect interpretation is worthy of mention because it often leads to the erroneous diagnosis of myocardial infarction.

The effect of anomalous conduction on the S-T segments and T waves is seen in Figs. 3*A*, *B*, and *C*. The striking changes are secondary to the altered order of ventricular excitation. The same phenomenon is illustrated in Figs. 12 and 13, which also reveal that anomalous conduction may conceal significant T wave abnormalities. The masking of abnormal S-T segment displacement is also demonstrated in Fig. 4. However, such displacement is not always concealed by anomalous conduction. It is evident in both the normal (dated April 30, 1952) and abnormal complexes (dated May 5, 1952) reproduced in Fig. 10. A diagnosis of infarction is often made, on insufficient evidence, we believe, on the type of S-T segment and T wave abnormalities seen in the tracing of May 5, 1952 (Fig. 10). Although a lesion is present in this case, the diagnosis is unwarranted because the characteristic QRS abnormalities indicative of infarction are absent. The S-T segment and T wave abnormalities assume reliable diagnostic significance only when the QRS signs of infarction emerge in the normally conducted beats. Convincing proof of the correctness of this point of view is exhibited by the electrocardiogram, from another patient, reproduced in Fig. 14. Conspicuous S-T segment and T wave abnormalities are present despite the complete absence of cardiac symptoms. Returning to Fig. 10, the small QRS deflections seen in V_6 are similar to those which occasionally occur in uncomplicated examples of anomalous conduction, and are not, therefore, diagnostic of infarction. The anomalous component is hardly recognizable as such, for although positive, its magnitude is very small. If not properly identified as the initial component of the QRS group, the large negative deflection which follows it must be considered as an abnormal Q wave, and therefore, as a sign of infarction.

Leads, in which the anomalous component is large and negative, display conspicuous Q waves or QS deflections. The latter commonly occur in esophageal leads at high levels,[3] in Leads II, III, and aV_F, and in the right-sided precordial leads. The premature component is easily identified in the limb leads in the upper row of Fig. 12. The QS deflections have no special significance, and occur in uncomplicated cases of the Wolff-Parkinson-White Syndrome as well as in those with posterior infarction. There are no distinguishing features in the two groups which serve to differentiate the QS deflections in those with infarction from those without it. Therefore, the diagnosis of posterior infarction solely on the basis of QS deflections in the anomalous complexes of the limb leads is not warranted. However, in the presence of infarction the QS deflections are replaced by conspicuous QR waves when anomalous conduction is interrupted (Figs. 4, 5, 9, 10, 12), while in those without this lesion normal QRS deflections take the place of the anomalous QS deflection. The latter is shown in Figs. 1, 2, and 3 of an earlier publication.[19]

TABLE II. EFFECT OF VARIOUS PROCEDURES ON ANOMALOUS CONDUCTION. CASE 3

DATE	CONTROL ELECTRO-CARDIOGRAM	PROCEDURE	EFFECT
4/25/52	Anomalous	0.9 mg. atropine intravenously	None
4/26/52	Anomalous	0.6 Gm. quinidine at 10:00 A. M.	None
		1.0 mg. atropine intravenously at 1:00 P. M.	None
4/28/52	Anomalous	Atropine 2.0 mg. subcutaneously at 11:39 A. M.	None
		Right and left carotid sinus stimulation at 11:46 A. M.	Sinus rate slowed from 65 to 45
		Right carotid pressure at 11:49 A. M.	Sinus rate slowed to 45
		Amyl nitrite inhalation at 12:45 P. M.	Sinus rate increased to 80
		1:00 P. M. observations ended	No change
4/29/52	Anomalous Q-T = 0.47″	Quinidine 0.9 Gm. orally at 11:00 A. M.	
		12:28 P. M.	Q-T = 0.52″
		Amyl nitrite inhalation at 1:15 P. M.	Normally conducted sinoauricular and A-V nodal beats-transient
		Amyl nitrite at 1:18 P. M.	Same as at 1:15 P. M. See Fig. 11
		Amyl nitrite at 1:19 P. M.	Same as at 1:15 P. M. and 1:18 P. M.
5/ 1/52	Anomalous	Atropine 3.0 mg. subcutaneously at 5:08 P. M.	
		Carotid sinus stimulation at 5:17 P. M.	None
		Sitting 5:20 P. M.	None
		Amyl nitrite inhalation at 5:55 P. M.	Sinus rate increased from 60 to 90
		Observations ended at 6:05 P. M.	None
5/ 2/52	Anomalous	Atropine 2.0 mg. intravenously at 11:25 A. M.	
		Carotid sinus stimulation at 11:27 A. M.	None
		Atropine 1.0 mg. intravenously at 11:37 A. M.	

TABLE II. (CONT.)

DATE	CONTROL ELECTRO-CARDIOGRAM	PROCEDURE	EFFECT
		Carotid sinus pressure	None
		Amyl nitrite inhalation at 11:45 A. M.	Sinus rate increased from 65 to 85
		Observations ended at 12:35 P. M.	None
5/ 7/52	Anomalous	Quinidine 1.2 Gm. at 11:00 A. M.	
		Forced respiration at 1:15 P. M.	Sinus premature beats
		Amyl nitrite at 1:27 P. M.	None
		Panting	None
		Amyl nitrite at 1:29 P. M.	A-V nodal rhythm for 45 seconds
		Amyl nitrite at 1:31 P. M.	None
		Carotid sinus stimulation	None
		Quinidine 0.3 Gm. at 1:50 P. M.	
		Forced respiration at 3:48 P. M.	Sinus premature beats
		Carotid sinus stimulation	None
		Observations ended at 3:50 P. M.	None
5/ 8/52	Anomalous	Quinidine 1.5 Gm. at 1:30 P. M.	
		3:50 P. M.	None
		Amyl nitrite inhalation at 4:15 P. M.	A-V nodal rhythm and normal intraventricular conduction
		Amyl nitrite	Same
		Amyl nitrite	Same
5/ 9/52	Anomalous	Quinidine 1.0 Gm. at 10:15 A. M.	None
		Quinidine 0.6 Gm. at 11:30 A. M.	None
		Amyl nitrite at 1:15 P. M.	A-V nodal rhythm and normal intraventricular conduction

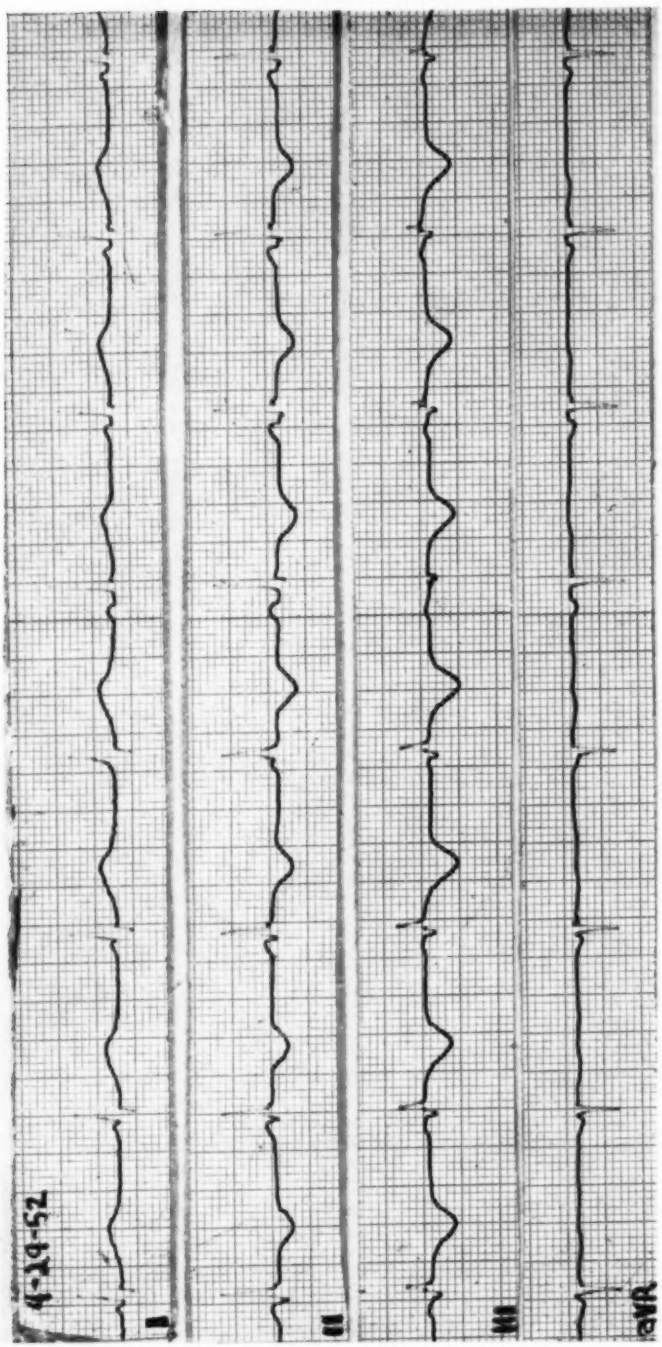

Fig. 11 (Case 3).—Simultaneous Leads I, II, III, and aV_R. 0.9 Gm. quinidine at 11:00 A. M. Tracing obtained at 1:18 P. M. during inhalation of amyl nitrite. Atrioventricular nodal rhythm and normal conduction in first four beats, sinoauricular rhythm and normal conduction in last three beats. Anomalous conduction and sinoauricular rhythm in fifth beat, the only one not displaying the signs of posterior infarction.

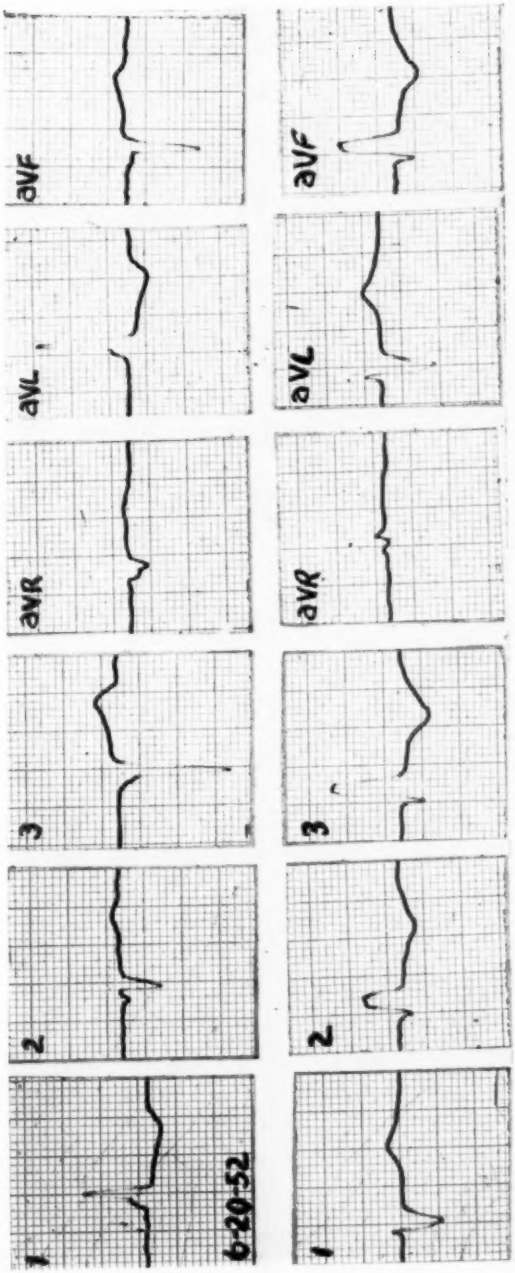

Fig. 12 (Case 4).—Top row: limb leads during anomalous conduction. Bottom row: limb leads during right bundle branch block. The latter display the signs of posterior infarction. Note the QS deflections in Leads II, III, and aV_F of the top row, and change in direction of the T waves in all leads when the mechanism changes.

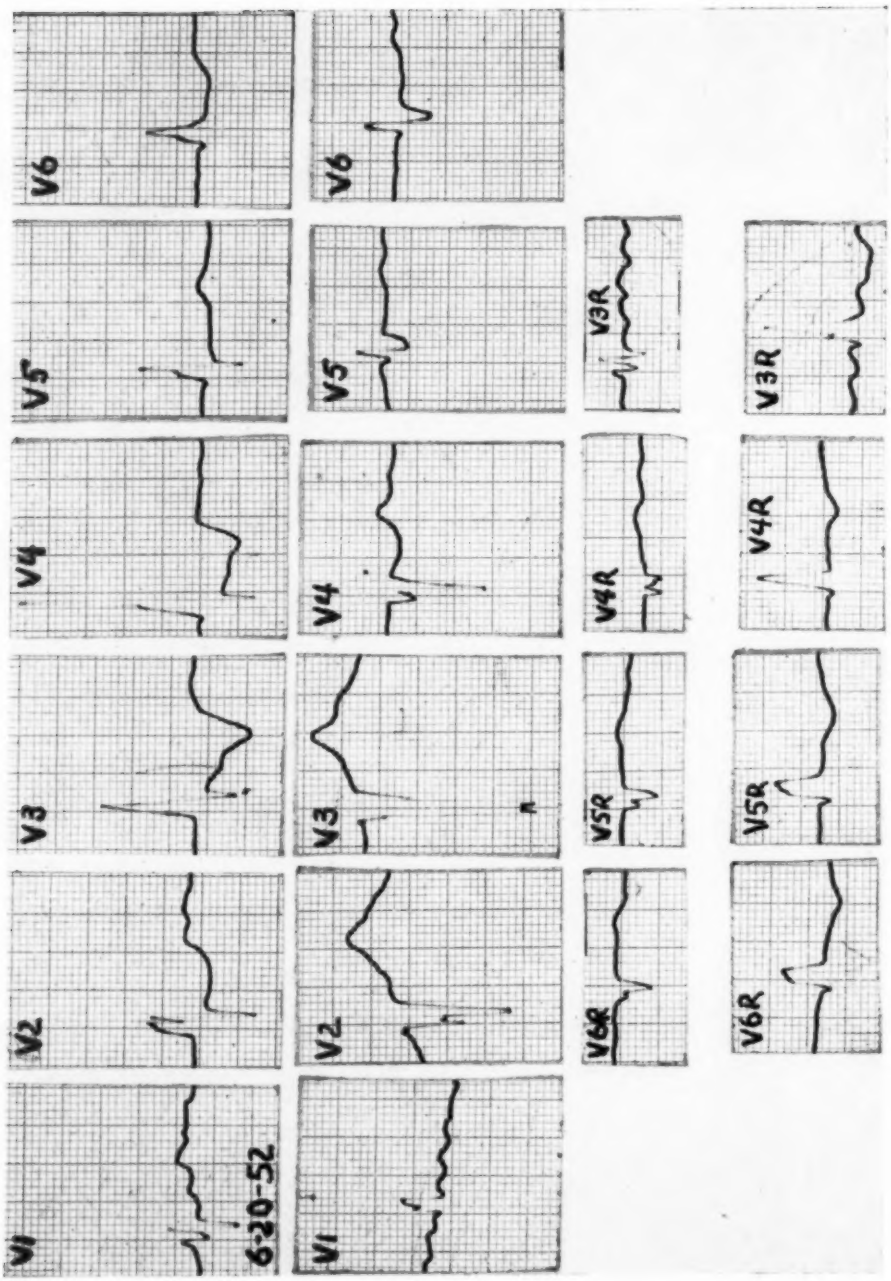

Fig. 13 (Case 4).—Top and third rows: precordial leads during anomalous conduction. Signs of infarction are absent. Second and bottom rows: precordial leads during right bundle branch block. Signs of anterior and posterior infarction are present.

During transitions from sinus to atrioventricular nodal rhythm, or the reverse, complexes may occur which display normal P waves, abnormally short P-R intervals, and the QRS signs of infarction. This is so whether the transitions occur spontaneously, or are induced by various procedures (Cases 2 and 3), and unless properly interpreted, may be the cause of confusion. Figure 9 displays a continuous strip of Lead II recorded after the intravenous injection of 0.9 mg. atropine. The first five beats in the upper strip display a short P-R interval with notched QS deflections, the sixth beat a short P-R interval and a conspicuous Q wave, followed by an R deflection. Signs of infarction appear in this complex, despite the short P-R interval, because the ventricle is responding to an atrioventricular nodal impulse, a rhythm which usually precludes anomalous conduction, and the P wave is normal and the P-R interval short because the auricle

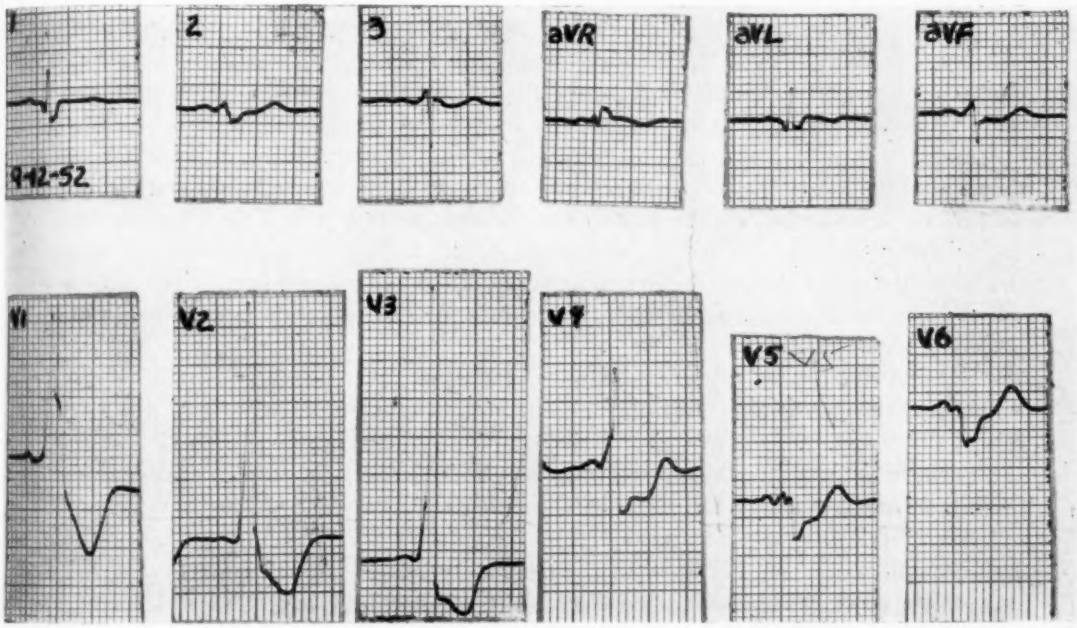

Fig. 14.—From a 69-year-old woman with a history of paroxysmal tachycardia, but no attacks for several years. Conspicuous S-T segment and T wave changes despite complete absence of cardiac symptoms. These changes were present over a long period of time with minor fluctuations.

is responding to a sinoauricular impulse. The gradual emergence of inverted P waves at increasingly greater intervals after the QRS complex confirms this interpretation. The bottom strip displays the gradual reversion to a mechanism in which the sinoauricular node is again the sole cardiac pacemaker, and again anomalous conduction and QS deflections appear. Figure 8 shows leads V_1 and V_6 from the same experiment.

A somewhat similar phenomenon is exhibited in Fig. 6. Anomalous conduction has been abolished by a single dose of quinidine, and right bundle branch block has taken its place. In spite of the gradual development (long strips) and maintenance of a short P-R interval (single complexes), the ventricular complexes

continue to display the signs of right bundle branch block, and of anterior and posterior myocardial infarction. This apparent paradox is explained by the fact that the short P-R interval is the consequence of atrioventricular nodal rhythm, and not of anomalous atrioventricular excitation. The reversal in direction of the P waves, which signifies displacement of the pacemaker from the sinoauricular to the atrioventricular node, is evident in some leads, but not in others; therefore, the change in rhythm might have been overlooked (Fig. 6). Subsequently, sinoauricular rhythm was re-established by carotid sinus stimulation and, coincidentally, anomalous atrioventricular excitation recurred. Therefore, the P-R interval remains abbreviated, the ventricular complexes assume the anomalous form, and the signs of infarction disappear (Fig. 7).

The first four complexes in Fig. 11 display signs consistent with posterior infarction, and are entirely different from the routine curves obtained on this patient. Nevertheless, the P waves are normal, and the P-R interval is short. Progressive shortening of the P-R interval, however, culminating in the almost complete disappearance of the P wave in the fourth complex, reveals that the ventricles are responding to atrioventricular nodal, and the auricles to sinoauricular impulses. As a consequence, anomalous atrioventricular excitation has been abolished, and the signs of infarction emerge. The last three ventricular complexes are similar, except that the ventricles are responding to auricular impulses (sinoauricular rhythm). The minor differences in the contour of the ventricular complexes during atrioventricular nodal rhythm have been observed by others and attributed to aberrant intraventricular conduction associated with atrioventricular nodal rhythm.[20]

The auricular rate of the first four, and the last three beats is identical. The fifth beat is premature, and the initial ventricular deflections are entirely different from all others in this tracing; the signs of infarction are completely absent. This single beat, in the four simultaneously recorded strips, displays anomalous atrioventricular excitation, demonstrating again that anomalous conduction masks the QRS signs of infarction. The recognition of anomalous conduction in this tracing is difficult, because the premature component barely departs from the isoelectric level; it is positive in Leads I and II, and negative in Lead III.

The diagnosis of anomalous conduction was made in Case 4 despite the existence of permanent auricular fibrillation. The vectorcardiogram is so distinctive that the diagnosis can be made without reference to the P-R interval, as will be described in a subsequent communication. As in Cases 1, 2, and 3, the signs of infarction are masked by anomalous conduction, but emerge when the latter is absent (Figs. 12 and 13). The occurrence of anomalous conduction during atrioventricular nodal rhythm is noteworthy and will be discussed in a subsequent communication.

THE INTERRUPTION OF ANOMALOUS CONDUCTION

Many measures temporarily interrupt anomalous excitation by abolishing the abnormal mechanism, or by altering the order of auricular excitation. The latter is most consistently achieved when the pacemaker shifts to the lower part of the atrioventricular node, and may be induced by carotid sinus stimulation,

the parenteral administration of atropine (vagotonic effect), and the inhalation of amyl nitrite. The former may be accomplished with quinidine, atropine (vagolytic effect), and deep inspiration. The abnormal mechanism can be functionally restored with carotid sinus stimulation, providing atrioventricular nodal rhythm is not thereby induced, and with digitalization. The cardiac mechanism can be altered in other ways,[15] but these measures alone were used in the experiments described above.

The ease with which anomalous conduction can be interrupted, as well as the measures required, varies from patient to patient, and from time to time in the same patient (Tables I and II). Atropine, in amounts up to 3.0 mg. injected intravenously, seldom abolishes anomalous conduction by virtue of its vagolytic action, even when amyl nitrite is added to enhance its effect (Cases 2 and 3). Also, it is usually ineffective when administered for its vagolytic effect in conjunction with quinidine (Cases 2 and 3). The vagotonic action of the drug, however, is more reliable as a method of inducing normal conduction. Atrioventricular nodal rhythm and normal intraventricular conduction, produced by the intravenous injection of the drug, appear in less than a minute, but last only a matter of seconds; both intervals are considerably longer when the subcutaneous route is used.

Carotid sinus stimulation alone may induce atrioventricular nodal rhythm and normal intraventricular conduction, but the effect is transient (Fig. 5). This procedure is particularly effective while the heart is under the increased vagal control produced by atropine.[3]

Although the combinations of atropine and quinidine, and atropine and amyl nitrite, failed to inhibit anomalous conduction (Cases 2 and 3), a normal mechanism was repeatedly induced by amyl nitrite inhalation following the administration of quinidine (Case 3, Fig. 11). This alone made it possible to observe the electrocardiographic signs of posterior myocardial infarction in Case 3, since quinidine and atropine separately, in large doses, and combined with other measures (Table II), proved ineffective.

The variable response to quinidine, when the drug is used alone, must be taken into consideration when attempting to inhibit anomalous conduction. Whether the drug will be more effective when administered in a single large dose, or in divided smaller doses, cannot be predicted, and if one method fails, the other should be used. The action of digitalis is of considerable importance, since it appears to stimulate and to perpetuate the anomalous mechanism, thus reducing the effectiveness of quinidine (Cases 1 and 2, Table I).

THE EFFECT OF DIGITALIS ON ANOMALOUS ATRIOVENTRICULAR EXCITATION

Opinions concerning the action of digitalis in the Wolff-Parkinson-White Syndrome are in conflict. Scherf and Shoenbruenner[21] noted an increase in the duration, then the disappearance, of the anomalous complexes, following the administration of digitalis, and concluded that the drug had a greater affinity for the anomalous than the normal atrioventricular pathways. Fox and associates[22] noted that the increase in the duration of the anomalous complex produced by

digitalis was abolished by atropine. They concluded that the action of digitalis was a vagal effect and that the drug had a greater affinity for the normal than the anomalous atrioventricular pathways. In a later publication Fox and Robb[23] observed the appearance of anomalous beats following digitalization. Wolff and White[1] noted morphologic changes in the anomalous complex following digitalization, which were not abolished by atropine, and observed a variable effect on the several electrocardiographic intervals, presumably dependent on the difference between the anomalous and normal atrioventricular conduction time. They also observed the failure of digitalis to block the anomalous mechanism in cases of auricular fibrillation with "fast runs" of anomalous beats; the latter were abolished by quinidine. These facts are inconsistent with the notion that digitalis suppresses the anomalous mechanism.

Anomalous complexes in Case 1 did not occur spontaneously, nor could they be induced with repeated stimulation of the carotid sinus, over a prolonged period of time. Following rapid oral digitalization, however, abnormal beats appeared spontaneously now and then, or could be induced to appear easily with carotid sinus stimulation. Twenty-one hours after digitalization was started anomalous conduction prevailed, but could be easily interrupted by a deep inspiration. At this time vagal control was extremely sensitive, conversion from one rhythm to the other being readily effected by carotid sinus stimulation or a deep inspiration. Forty-eight hours later normal conduction was firmly re-established, and repeated attempts to induce anomalous conduction with carotid sinus stimulation and the Valsalva experiment failed. Four hours after a single additional dose of 0.4 mg. digitoxin, however, anomalous conduction reappeared, and it was again possible to elicit either type of conduction at will. A single observation a few months later revealed the presence of normal conduction.

The data in Case 2 suggest a similar relationship between digitalization and anomalous conduction.

These data cannot be explained without assigning an important role to vagal control in anomalous conduction. Although there is suggestive evidence that digitalis affects anomalous conduction by a direct action,[1] as well as through its effect on vagal tone, vagal control alone is responsible for the effects of digitalis observed in Case 1. This drug apparently produced a critical level of vagal tone so that the slightest increase (carotid sinus stimulation) induced anomalous conduction, and the slightest decrease (deep inspiration) abolished the abnormal mechanism. This critical level, once attained, was maintained for several hours.

SUMMARY

Anomalous atrioventricular excitation produces changes in the QRS complex which simulate myocardial infarction, and it conceals the presence of myocardial infarction by preventing the development of the QRS abnormalities which are diagnostic of this lesion. The anomalous order of ventricular excitation also produces changes in the S-T segments and T waves, which are characteristically unstable in this syndrome. Changes dependent on physiologic, or other, unknown influences, commonly occur. It is not possible to distinguish such changes from

those which follow infarction of the myocardium. Moreover, similar S-T segment and T wave abnormalities occur with other types of injury and with other pathologic states, or may occur following the administration of certain drugs. These signs, then, cannot be considered reliable evidence of myocardial infarction.

All these facts are important in the management of patients whose electrocardiograms display anomalous atrioventricular excitation. Error can be avoided only if great care is taken to recognize anomalous conduction, and then to refrain from making a diagnosis of infarction unless normally conducted beats* occur, or can be induced. Carotid sinus stimulation, atropine, quinidine, and amyl nitrite, separately, or in combination, usually suffice to restore normal conduction. Failure with a given drug or measure on one occasion may be followed by success on another. The amount and rapidity of administration of drugs may be varied. The effect of digitalis in facilitating the appearance of, or in perpetuating the continuance of the anomalous mechanism, may explain failure to induce normal conduction in some cases. When feasible, efforts to convert the cardiac mechanism should be attempted before digitalis is administered, or, when it can be done without harm to the digitalized patient, the drug should be omitted when it seems impossible to abolish anomalous conduction otherwise.

CONCLUSIONS

1. Four cases of myocardial infarction in which the electrocardiograms displayed both normal and anomalous atrioventricular excitation have been presented in detail. The electrocardiographic signs of myocardial infarction were evident when normal conduction prevailed, but were masked by anomalous excitation.

2. The common causes of error in the diagnosis of myocardial infarction in patients with the Wolff-Parkinson-White Syndrome have been discussed.

3. Error may be inevitable if anomalous conduction is not recognized.

4. Error can be avoided by refraining from making a diagnosis of infarction when the sole mechanism is that of anomalous conduction.

5. Conversion to normal conduction can be effected with carotid sinus stimulation, deep inspiration, quinidine, atropine, and amyl nitrite, separately or in combination.

6. Digitalis favors the anomalous mechanism, and should be withheld until conversion to normal conduction is accomplished, or withdrawn when the abnormal mechanism appears to be fixed.

REFERENCES

1. Wolff, L., and White, P. D.: Syndrome of Short P-R Interval With Abnormal QRS Complexes and Paroxysmal Tachycardia, Arch. Int. Med. **82**:446, 1948.
2. Wolff, L.: Electrocardiography: Fundamentals and Clinical Application, Philadelphia, W. B. Saunders Company, 1950. Fig. 106 and p. 178.
3. Rosenbaum, F. F., Hecht, H. H., Wilson, F. N., and Johnston, F. D.: The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), Am. Heart J. **29**:281, 1945.
4. Pondé, Adriano de Azevedo, and Pondé, Alberto de Zevedo: Excitacao Atrioventricular Anomala, São Salvador, Brazil.

*Or right bundle branch block; since this conduction defect does not mask the signs of infarction.

5. Eichert, H.: Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction, Ann. Int. Med. **21**:907, 1944.
6. Goldbloom, A. A., and Dumanis, A. A.: Short P-R Interval With Prolongation of QRS Complex and Myocardial Infarction, Ann. Int. Med. **25**:362, 1946.
7. Rinzler, S. H., and Travell, J.: Electrocardiographic Diagnosis of Acute Myocardial Infarction in the Presence of the Wolff-Parkinson-White Syndrome, Am. J. Med. **3**:106, 1947.
8. Wendkos, M. H., and Nadler, C.: Observations Concerning the Instability of the T Wave in Wolff-Parkinson-White Syndrome, Proc. Am. Fed. Clin. Res. **3**:62, 1947.
9. Littman, D., and Tarnover, H.: Wolff-Parkinson-White Syndrome, Am. Heart J. **32**:100, 1946.
10. Tamagua, I. G., Butterworth, J. S., and Poindexter, C. A.: Wolff-Parkinson-White Syndrome With Myocardial Infarction: An Experimental Study, Am. Heart J. **35**:948, 1948.
11. Kistin, A. D., and Robb, G. P.: Modification of the Electrocardiogram of Myocardial Infarction by Anomalous Atrioventricular Excitation: Report of a Case, Am. Heart J. **37**:249, 1949.
12. Wolff, L.: Electrocardiography: Fundamentals and Clinical Application. Philadelphia, 1950, W. B. Saunders Company, pp. 180-182.
13. Levine, H. D., and Burge, J. C.: Septal Infarction With Complete Heart Block and Intermittent Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome): Histologic Demonstration of a Right Lateral Bundle, Am. Heart J. **36**:431, 1948.
14. Stein, I., and Wroblewski, F.: Myocardial Infarction in Wolff-Parkinson-White Syndrome, Am. Heart J. **42**:624, 1951.
15. Dressler, W., and Roesler, H.: An Atlas of Electrocardiography, Springfield, Ill., 1949, Charles C Thomas, p. 424.
16. Goldberg, H. H., and Lewis, S. M.: Acute Myocardial Infarction and the Wolff-Parkinson-White Syndrome, Am. Heart J. **40**:614, 1950.
17. Zoll, P. M., and Sacks, D. R.: Myocardial Infarction Superimposed on Short P-R, Prolonged QRS Complex, Am. Heart J. **30**:527, 1945.
18. Fischer, R.: Influence d'une thrombose coronarienne aigue sur l'electrocardiogramme d'un bloc de branches, Arch. mal. coeur **31**:397, 1938.
19. Wolff, L., Parkinson, J., and White, P. D.: Bundle Branch Block With Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, Am. Heart J. **5**:685, 1930.
20. Wilson, F. N.: A Case in Which the Vagus Influenced the Form of the Ventricular Complex of the Electrocardiogram, Arch. Int. Med. **16**:1008, 1915.
21. Scherf, D., and Schoenbruenner, E.: Beitrage zum Problem der Verkurzten Verhofkaminer-Leitung, Ztschr. f. klin. Med. **128**:750, 1935.
22. Fox, T. T., Travell, J., and Molofsky, L.: Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, Arch. Int. Med. **71**:206, 1943.
23. Fox, T. T., and Robb, A. L.: On the Mechanism of the Electrocardiographic Syndrome of Short P-R Interval With Prolonged QRS Complex, Am. Heart J. **28**:311, 1944.

HISTOLOGIC STUDIES OF THE INTERNAL MAMMARY ARTERY AFTER IMPLANTATION INTO THE MYOCARDIUM

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THE internal mammary artery after implantation into the left ventricular myocardium of the dog develops new branches. These newly developed branches enter the myocardium and form a connection with the left coronary circulation. This fact has been proved by injection studies, serial sections, plastic casts, and physiologic evidence.[1,2,3] When a large anastomosis exists between the implanted internal mammary artery and the left coronary circulation it protects against death and infarction after sudden ligation of the anterior descending branch of the left coronary artery.[4]

Chronic coronary artery insufficiency has been experimentally produced and successfully treated by an internal mammary artery implant.[5] In spite of the functional evidence of the value of an internal mammary artery implant, some doubts have been raised as to the size of the anastomosis and as to its duration. Glenn and associates[6] suggested that the new branches were composed of granulation tissues, and like granulation tissue they tended to disappear at the end of six weeks. Shortly after the publication of Glenn's paper, we re-examined our serial sections in order to determine the duration and character of the internal mammary coronary anastomosis.

DURATION OF ANASTOMOSIS

The data shown in Table I indicate that there has been no tendency for an anastomosis to disappear at the end of six weeks. Actually the average duration of anastomosis studied by us was eleven weeks. One of our animals was sacrificed at the end of fifty-eight weeks and a large functional anastomosis proved.

HISTOLOGIC STUDIES

In this paper re-examination of serial sections of coronary-mammary anastomoses in seven different animals is reported. The shortest time after implant was twelve weeks and the longest was fifty-eight weeks. In two animals, Number 6 and Number 8, respectively, the original sections were restained by special techinques. The objective of the histologic studies was to determine whether or not the branches of the implanted internal mammary artery were simple granulation capillaries or had become vessels of a higher order.

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TABLE I. DURATION OF ANASTOMOSIS

TYPE OF ANASTOMOSIS	NO. OF ANIMALS	PRESENCE OF ANASTOMOSIS AFTER IMPLANT (WK.)	VALUE OF ANASTOMOSIS AFTER LIGATION OF ANT. DESC. BRANCH LT. CORONARY ARTERY
Microscopic Anastomosis	1	5	Protection against death or infarction afforded in 3 animals only.
	1	6	
Anastomosis small due to thickened or partially thrombosed internal mammary artery.	1	7	
	2	8	
	2	11	
	2	12	
	2	13	
	1	14	
	12		
Macroscopic Anastomosis	1	6	No deaths or infarction occurred.
	2	7	
Anastomosis large, internal mammary artery patent.	5	9	In "Cellophane-coronary artery-sclerosis" caused* by Cellophane irritation marked improvement in exercise tolerance occurred.
	5	11	
	4	12	
	2	14	
	1	17	
	1	18	
	3	19	
	1	21	
	1	31	
	1	41	
	1	46	
	1	58	
	29		

*Submitted for publication.

In order to study the nature of the wall of arterial branches, the following stains were used: (a) Masson trichrome; (b) Hemalum, Phloxin, Saffron. Both stains (a) and (b) were combined with Weigert's elastic stain. (c) Mallory's phosphotungstic acid and hematoxylin. These stains all show smooth muscle, collagen, and elastic fibers with great specificity.

Newly formed arteries have certain definite histologic characteristics. These are most evident in the newly formed muscular and elastic coats. Using the usual hematoxylin-eosin stain, it may be very difficult to differentiate between smooth muscle, collagen fibers and elastic fibers. These structures however are clearly demonstrated by the above mentioned special stains. Thus, it has been possible to visualize and to assess the exact nature of the various structures which compose the wall of newly formed branches of the implanted internal mammary artery.

OBSERVATIONS

The serial sections prestained by hematoxylin-eosin of the implanted internal mammary artery were re-examined in seven different animals. The internal mammary artery in each case had branched. A large branch or branches

could be followed in the serial section into the ventricular myocardium away from the parent vessel. As we have mentioned the hematoxylin-eosin stains did not differentiate the various structures in the arterial walls. Because of this it was impossible to state with certainty that the structures which were seen leaving the internal mammary artery were similar to arterial branches. Deductive evidence based on functional studies and casts made of the anastomoses indicated that these branches were newly formed.

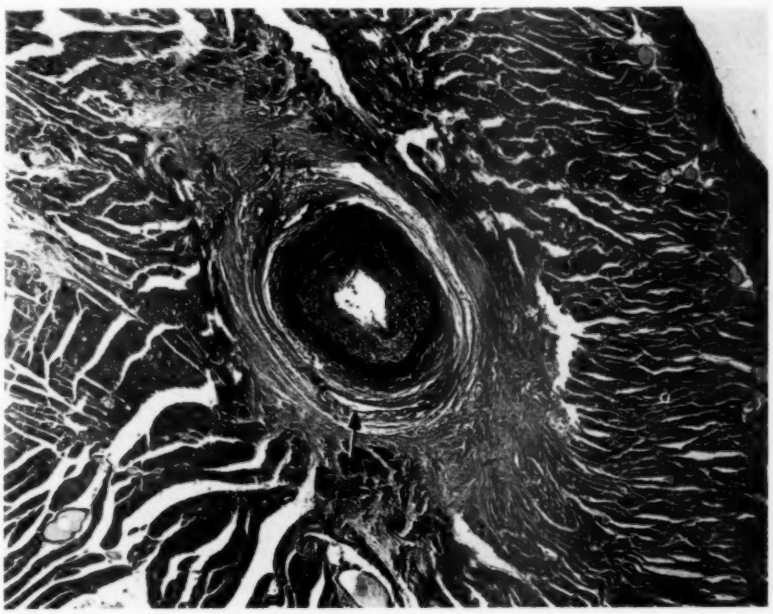

Fig. 1.—(Dog Number 8.) Section of implanted mammary artery four months after implantation. Note the branches (see arrow). These have been followed by a serial section into the myocardium. They have been shown to be arteries containing elastic tissue and a muscle coat. Note the absence of reaction around the implant and the maturity of the collagen fibers in its vicinity. It has apparently reached its maximum state of contraction.

The serial sections of dogs Numbers 6 and 8 stained originally with hematoxylin-eosin were restained by the special aforementioned stains to show the characteristics of the vessels. A study of the sections showed that the branches of the implanted internal mammary arteries which had been followed in the hematoxylin-eosin stains were newly formed arterial branches. The walls of these vessels contained a muscular coat composed of several muscle cell layers intermingled with elastic and collagen fibres. The lumen to wall-thickness ratio was about 6:1. This was found to be true in dog Number 8 after four months of implantation (Figs. 1 and 2) and dog Number 6 approximately thirteen months after implantation.

The internal mammary arteries examined were lying in the myocardium and seemed to excite very little reaction around them. The small amount of scar tissue present which surrounded the implant appeared to have reached full maturity and thus it would seem had reached its maximum of contraction.

Histologic studies of these sections make it seem improbable that the implanted internal mammary artery with its branches would become occluded by contraction of the perivascular scar tissue. In this respect, the newly formed branches differ from those vessels that are formed in granulation tissues and tend to disappear with the lapse of a relatively short period of time. Moreover their structure is more highly organized than the vessels found in simple granulation tissue.

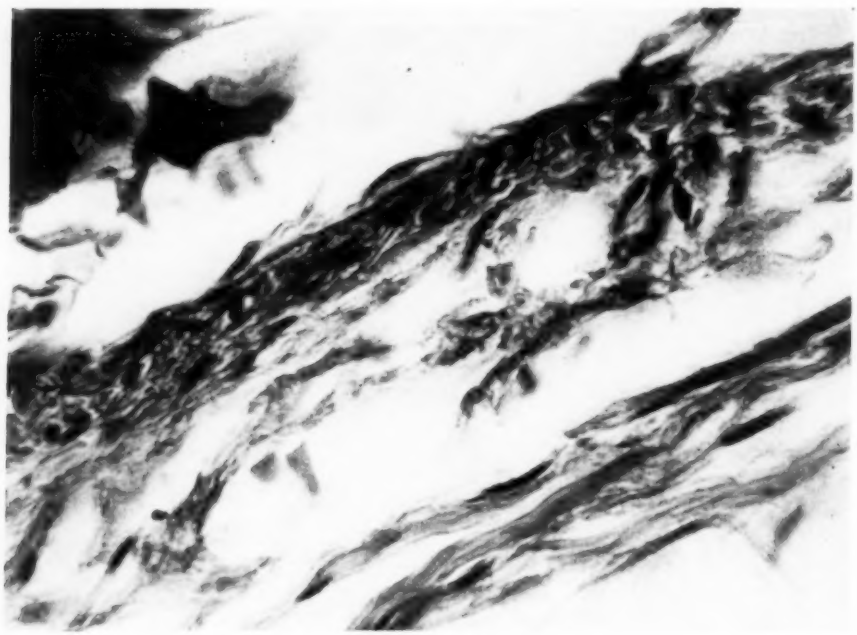

Fig. 2.— (Dog Number 8.) A high power microscopic view of the branch shown at 7 o'clock in Fig. 1. This shows the structure of the wall of the new branch of the internal mammary artery. Note the elastic tissue and double layer of muscle cells.

CONCLUSIONS

Our recent histologic studies confirm the previous physiologic and histologic studies made on internal mammary artery implants. There is no doubt that the internal mammary artery branches after implantation into the ventricular myocardium. These branches develop into true arteries containing elastic tissue and muscular coats within their walls, and like the ramification of the coronary arteries can be traced until they disappear between the muscle fibers of the ventricular myocardium. Our findings do not support Glenn's[6] observation that these new branches of the implanted mammary artery are similar to the vessels of granulation tissue and tend to disappear at the end of six weeks.

REFERENCES

1. Vineberg, A. M.: Development of Anastomoses Between Coronary Vessels and Transplanted Internal Mammary Artery, Canad. M. A. J. **55**:117, 1946.

2. Vineberg, A. M., and Jewett, B. L.: Development of an Anastomosis Between the Coronary Vessels and a Transplanted Internal Mammary Artery, Canad. M. A. J. **56**:509, 1947.
3. Vineberg, A. M.: Development of an Anastomosis Between Coronary Vessels and Transplanted Internal Mammary Artery, J. Thoracic Surg. **6**:839, 1949.
4. Vineberg, A. M., and Niloff, P. H.: The Value of Surgical Treatment of Coronary Artery Occlusion by Implantation of the Internal Mammary Artery Into the Ventricular Myocardium, Surg., Gynec. & Obst. **91**:551, 1950.
5. Vineberg, A. M., Niloff, P. H., and Miller, D.: Treatment of Coronary Artery Insufficiency by Implantation of the Internal Mammary Artery Into the Left Ventricular Myocardium, Proc. Roy. Coll. Physicians and Surgeons, Canada, Montreal, December, 1950.
6. Glenn, F., Hulswade, G., and Gore, Arthur L.: Surgical Forum Clinical Congress of the American College of Surgeons, Philadelphia 1950. W. B. Saunders Company, p. 289-293.

COMPARATIVE EFFECTS OF 3-HYDROXY-2-PHENYLCINCHONINIC ACID (HPC) AND ASPIRIN ON THE ACUTE COURSE OF RHEUMATIC FEVER AND THE OCCURRENCE OF RHEUMATIC VALVULAR DISEASE*

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IN JULY of 1950 Blanchard and associates[1] reported a favorable effect upon the fever and arthritis of acute rheumatic fever when a product closely related to cinchophen, 3-hydroxy-2-phenylcinchoninic acid (HPC), was employed therapeutically. Pharmacologic investigation of the drug in man and animals had indicated that the action of HPC was like adrenocorticotrophin and that the drug perhaps stimulated the production of ACTH.[1,2] An investigation of the comparative effects of HPC† and aspirin on the acute course of rheumatic fever and on the occurrence of rheumatic valvular heart disease is the subject of this report.

DESCRIPTION OF STUDY

From January to June, 1951, all airmen admitted to this hospital with a tentative diagnosis of rheumatic fever were placed in a study ward and observed daily by one of two physicians. The criteria employed for the diagnosis of rheumatic fever were essentially those of Jones[3] except for the classification of an abnormal P-R interval as a minor rather than a major manifestation. Although a patient's illness satisfied the diagnostic criteria for rheumatic fever, certain indications of activity had to be present at the time therapy was initiated. These indications were the presence of either a major manifestation or two of the three minor manifestations included in Table I.

Following the institution of therapy, daily observations by the same observer were continued for at least nine weeks. Rectal temperatures were taken every

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†HPC was furnished through the courtesy of Sharp & Dohme, Inc., Philadelphia, Pa., and Eli Lilly & Company, Indianapolis, Ind.

four hours. Sleeping pulse, blood pressure, and weight were recorded daily. Electrocardiograms were obtained daily for the first three weeks and every other day for the remainder of the nine weeks' period. Erythrocyte sedimentation rates were done by the Wintrobe method three times weekly during the first three weeks and the week following the cessation of treatment; at all other times they were done once each week unless they were found to be abnormal in which case they were done three times weekly until normal. Teleoroentgenograms were taken on admission to the study and weekly thereafter for nine weeks. Serum for antistreptolysin "O" titers and throat cultures for beta hemolytic streptococci were obtained every ten days for the first nine weeks. The presence of C-reactive protein* was determined by the method of Anderson and McCarty[4] in three serum specimens obtained from each patient at ten day intervals—the first of the serial specimens was obtained during the last week of treatment. After the first nine weeks, follow-up examinations were done at monthly intervals. Physical examinations and histories were obtained to ascertain whether or not any patient had had an intervening streptococcal infection, renewed rheumatic activity, or any change in physical status. Complete blood count, urinalysis, electrocardiogram, sedimentation rate, throat culture, and a serum specimen for antistreptolysin titer were obtained at the monthly follow-up. Chest roentgenograms were repeated at six and twelve months.

TREATMENT SCHEDULES

Selection of treatment for each patient was accomplished by opening a serially numbered envelope which corresponded to the patient's assigned study number.†

The total daily dose of HPC was 20 mg. per kilogram of body weight. This total dose was divided into three equal doses and administered at hourly intervals as recommended by Marshall and associates.[2]

For the first forty-eight hours the total daily dose of aspirin was one grain per pound of body weight with no total daily dose exceeding 150 grains. During the following five days the total daily dose was two-thirds grain per pound and for the following five weeks the dose was one-half grain per pound per day. Aspirin was given every four hours for the first forty-eight hours and every six hours thereafter.

Both HPC and aspirin were administered for a total of six weeks. If three weeks after cessation of treatment any patient still met the criteria for rheumatic activity, treatment was reinstituted with the same drug and dosage but continued for only four weeks. To eradicate the streptococcal carrier state all patients received penicillin, 600,000 units in oil, on the day of admission to the study and every three days for a total of four injections. Following this course of penicillin

*The authors are indebted to Dr. Maclyn McCarty of the Rockefeller Hospital for the immune rabbit serum used in determining the presence of the C-reactive protein.

†These envelopes were prepared and sealed prior to the beginning of the study by Miss Marjorie Bellows, Statistician, American Heart Association.

they received one gram of sulfadiazine daily for the remainder of the study period.* The patients were kept at bed rest for a minimum of nine weeks. If at the end of that time their disease was considered to be inactive, they were rehabilitated and allowed to pursue a normal active life.

COMPARABILITY OF THE TWO TREATMENT GROUPS

Sixty-nine patients met the established criteria for the diagnosis of rheumatic fever. Thirty-four were treated with HPC and thirty-five were treated with aspirin. One patient receiving aspirin developed hypoprothrombinemia which necessitated discontinuance of the drug on the seventh day of treatment. This patient has been excluded from the analysis. Comparison of the two groups reveals that they were comparable at the time treatment was started (Table I).

TABLE I. COMPARABILITY OF THE TWO TREATMENT GROUPS AT THE TIME THERAPY WAS INSTITUTED

	HPC	ASPIRIN
Number of Patients	34	34
Average Age at Onset of Rheumatic Fever	20.5	20.1
Average Day of Illness	8.6	8.4
Median Day of Illness	6	6
Major Manifestations:		
Number of Patients with		
1. Carditis	2	6
a. Development of or change in murmur	2	4
b. Change in heart size	0	0
c. Pericarditis	0	1
d. Failure	0	1
2. Polyarthritis	32	32
3. Chorea	0	0
4. Subcutaneous nodules	0	0
5. Erythema marginatum	1	1
Minor Manifestations:		
Number of Patients with		
1. Fever	23	22
2. Abnormal erythrocyte sedimentation rate	29	26
3. Abnormal auriculoventricular conduction	12	12
Rheumatic Fever History:		
Number of Patients with		
1. Personal history of rheumatic fever	7	9
2. Personal history of heart murmur	1	3
3. Family history of rheumatic fever	3	5
Number of Patients with Rheumatic Heart Disease	1	0

Results During the Acute Illness

Figure 1 indicates the per cent of patients in each group with fever (100°F. or above rectally) before, during, and after treatment. The incidence of fever at four-hourly intervals is presented for the day prior to and for the four days after the start of treatment; for the remainder of the

*This dosage was later increased to one and one-half grams daily.

observation period, the incidence of fever is presented at daily intervals. Approximately 70 per cent of each group had fever prior to institution of therapy. Within four hours after the start of treatment a fifty per cent reduction in the incidence of fever had occurred in the group receiving aspirin. Although the proportion of patients having fever decreased rather rapidly in the first thirty-six hours in both groups, the rate of decrease was more rapid in the aspirin-treated group. During the remainder of the observation period the percentage of patients with fever was similar in the two groups.

The occurrence of joint signs during the period of observation is presented in Fig. 2. The increase in incidence of objective joint findings occurring in the aspirin group after the eighth day was coincidental with the decrease in the total daily dose of aspirin. When arthralgia is also considered, the difference between the two groups which is apparent in Fig. 2 is not altered except for the appearance of a relatively greater increase of arthralgia after treatment in the HPC group. Those patients treated with HPC who continued to have joint signs during treatment rarely had severe joint involvement, but usually had only tenderness of the involved joint or joints. The

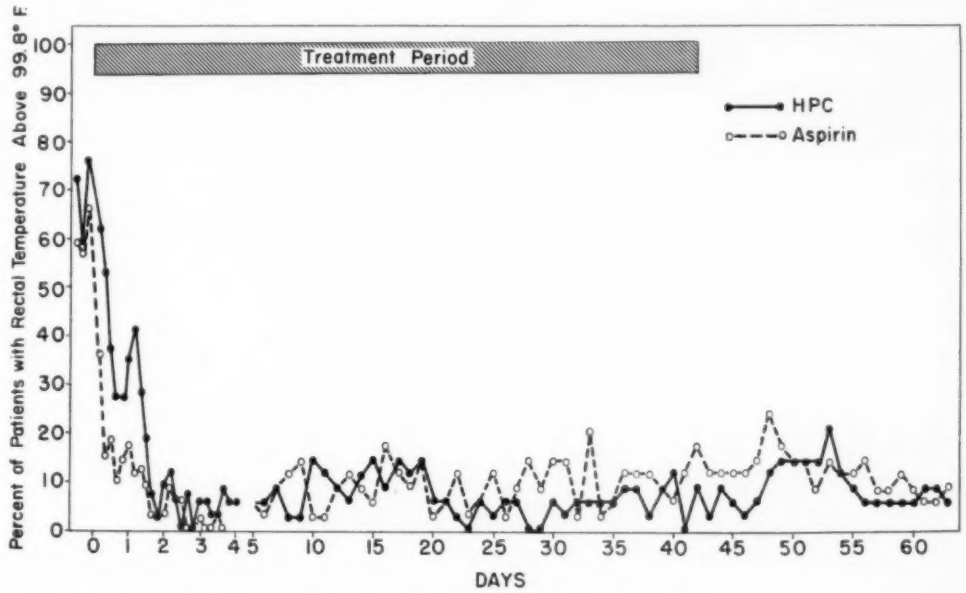

Fig. 1.—The effect of HPC and aspirin on fever.

number of patients who continued to develop symptoms or signs in previously uninvolved joints after the start of treatment was much less among those patients treated with aspirin than in those treated with HPC (Fig. 3). After the third day of treatment there is a marked difference between the two groups: a relatively large number of patients receiving HPC continued to develop new joint involvement. Among the patients represented in Fig. 3 almost all of the HPC-treated patients continued to have symptoms in multiple joints in contrast to the aspirin-treated patients who usually had persistence of pain in only a single joint.

The incidence of abnormal sedimentation rates at the beginning of treatment and for eleven weeks thereafter is shown in Fig. 4. After the first week of treatment a rather sharp decrease in incidence occurred, and it appeared to be more rapid in those patients treated with aspirin. Following the cessation of treatment the incidence of abnormal sedimentation rates became equal.

During the first week of treatment, the weight loss exhibited by the men in each treated group was similar. The average weight of the group of aspirin-treated patients increased during the

second week, but did not attain the pretreatment level until the fourth week. Gain in average weight did not occur in the HPC-treated patients until the third week and the pretreatment level was not reached until the fifth week. At the end of the thirteen weeks the weight gain in the aspirin group expressed as per cent increase over the average weight at the beginning of treatment was 6.7 per cent compared to 2.1 per cent in the HPC group.

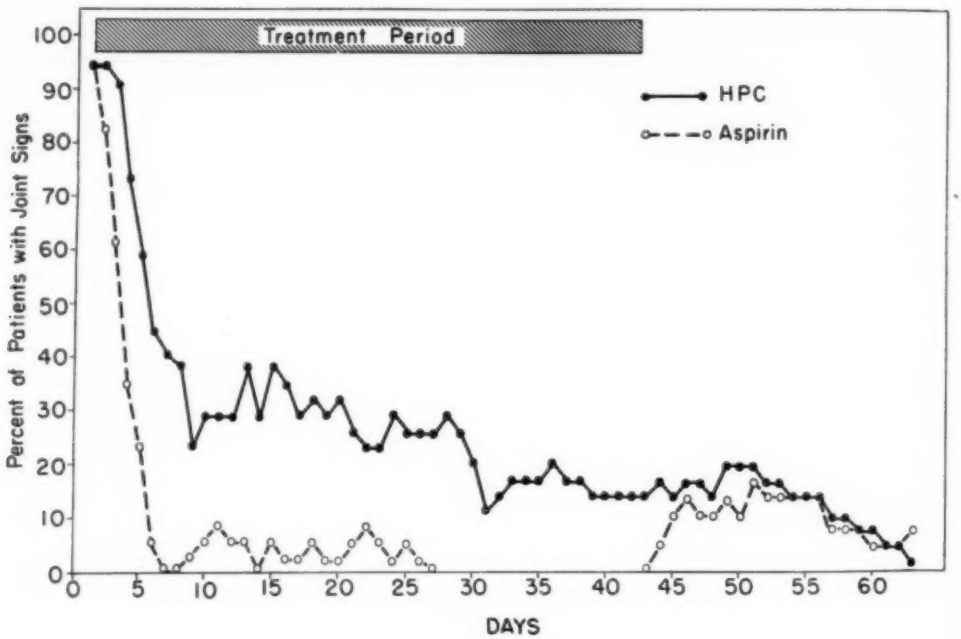

Fig. 2.—The effect of HPC and aspirin on objective joint findings.

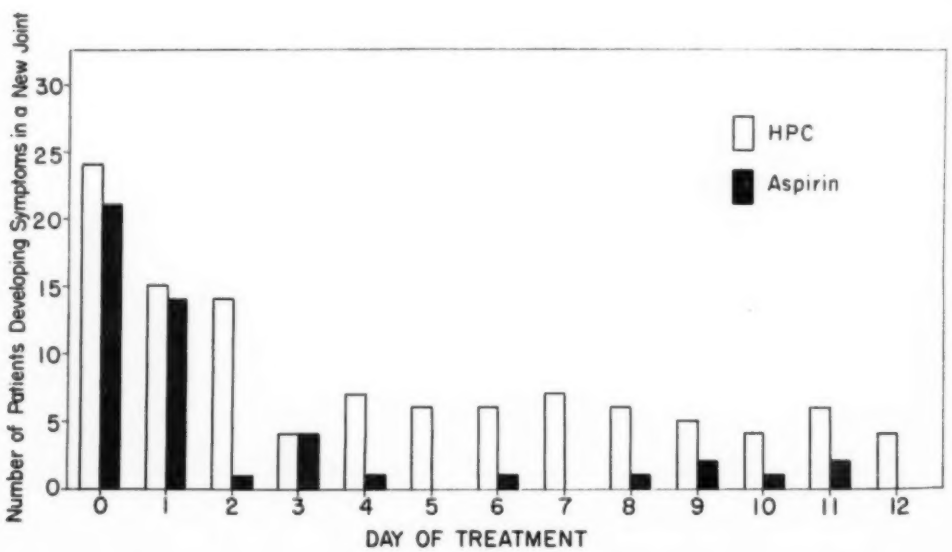

Fig. 3.—Symptoms or signs appearing in a joint which previously had been asymptomatic.

The only patient having cardiac failure at the start of treatment improved rapidly on aspirin therapy. Cardiac failure occurred in only one other patient, several months after a second course of treatment with HPC. One patient had a pericardial friction rub which disappeared six days after the start of aspirin therapy. During therapy none of the men treated with aspirin developed pericarditis. However, during the first week of treatment, three patients in the HPC-treated group developed pericardial friction rubs which persisted for one, seventeen, and twenty-one days. Two patients, one from each treated group, developed pericardial friction rubs for the first time nine days after the end of therapy. Cardiac enlargement was not a common finding in either group of patients. The average heart size in each group decreased approximately seven per cent after one week of therapy and thereafter there was no significant change in either group.

Abnormal auriculoventricular conduction occurred with equal frequency in the two series of patients (Table II). A normal conduction time usually appeared within ten days from the time the abnormal conduction was first observed. None of the HPC-treated patients had an abnormal conduction time throughout the treatment period; three aspirin-treated patients, however, had prolonged P-R intervals throughout the nine-week period of observation. After treatment two patients from the HPC group and four patients from the aspirin group developed prolonged P-R intervals.

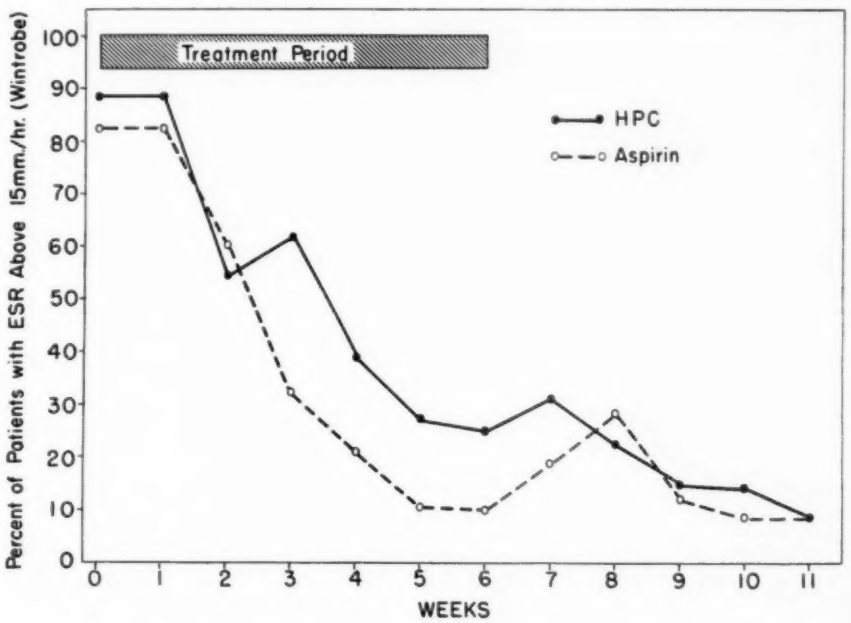

Fig. 4.—The effect of HPC and aspirin on the erythrocyte sedimentation rate.

During the acute illness, systolic murmurs were recorded as being either functional, questionably significant, or significant. This classification was based on the location, intensity, duration, constancy, and persistency of the murmurs. The observers, cognizant of the difficulties encountered in evaluating murmurs present during acute rheumatic fever, achieved satisfactory comparability in the classification of murmurs for the purpose of this study by making multiple and independent observations on the same patients. For the purposes of analyzing and comparing the occurrence of murmurs in the two treatment groups during the acute illness (Table III), a systolic or diastolic murmur was not considered significant unless it was recorded as significant on at least seven consecutive daily examinations. The number of patients with or without murmurs at nine weeks, the end of the period of daily observation, in relation to the presence or absence of murmurs at the beginning of treatment is presented in Table III. These data reveal

TABLE II. PATIENTS WITH ABNORMAL AURICULOVENTRICULAR CONDUCTION*

	HPC	ASPIRIN
Abnormal conduction prior to treatment	12	12
Abnormal conduction appearing for the first time after the start of treatment	8	7
Total	20	19

*Either a P-R interval measuring .22 second or greater, incomplete, or complete block.

that of those patients in each series who had significant murmurs at nine weeks, about one-half developed them after treatment started. In this respect, there appears to be no difference between those patients with a previous history of rheumatic fever and those patients experiencing their initial attack of this disease.

The occurrence of diastolic murmurs is of particular interest. Only one patient who was treated with aspirin had a diastolic murmur prior to treatment. This murmur was mid-diastolic in time and was heard at the apex where a moderately loud systolic murmur was also present. He had a history of previous rheumatic fever, but it was not certain at the onset of treatment whether these murmurs represented old rheumatic valvular disease or were the result of his present episode of rheumatic fever. He developed an aortic diastolic murmur which persisted; with the disappearance of the apical mid-diastolic murmur, a presystolic murmur appeared. Follow-up examinations indicated that this latter murmur was a murmur of mitral stenosis rather than an Austin Flint murmur. There were six additional patients in the aspirin group who developed diastolic murmurs during treatment; two had basal diastolic murmurs and four had mitral mid-diastolic murmurs. At the end of nine weeks these murmurs had disappeared in five cases while

TABLE III. SIGNIFICANT MURMURS* PRESENT NINE WEEKS AFTER THE START OF TREATMENT IN RELATION TO THE PRESENCE OF MURMURS AT THE BEGINNING OF THERAPY

	HPC (34 PATIENTS)			ASPIRIN (34 PATIENTS)		
	PREVIOUS HISTORY OF RHEUMATIC FEVER	NO PREVIOUS HISTORY OF RHEUMATIC FEVER	TOTAL	PREVIOUS HISTORY OF RHEUMATIC FEVER	NO PREVIOUS HISTORY OF RHEUMATIC FEVER	TOTAL
Number of patients with murmur at nine weeks	4	12	16	3	17	20
No murmur present at the start of treatment	1	6	7	0	10	10
Murmur present at the start of treatment	3	6	9	3	7	10
Number of patients with no murmur at nine weeks	3	15	18	6	8	14
No murmur present at the start of treatment	3	15	18†	5	7	12†
Murmur present at the start of treatment	0	0	0	1	1	2

*As defined in text.

†Two of these patients developed significant murmurs after treatment was started but the murmurs had disappeared by nine weeks.

TABLE IV. THE PERSISTENCE OR APPEARANCE OF SYMPTOMS AND SIGNS AFTER THERAPY WITH HPC WAS DISCONTINUED

PATIENT	JOINT MANIFESTATIONS		ABNORMAL ESR		C-REACTIVE PROTEIN		MAXIMUM TEMPERATURE AFTER THERAPY*	OTHER†
	AT THE END OF THERAPY[x]	AFTER THERAPY[xx]	AT THE END OF THERAPY[x]	AFTER THERAPY[xx]	LAST WEEK OF THERAPY	AFTER THERAPY		
W-4018	+	++	+	++	+	++++	102.8°	b, c
W-5002	+	++	0	++	0	++++	102.6°	b
W-4063	0	++	0	++	+	+++++	104.0°	0
W-4075	0	++	+	+	+	0	100.6°	0
W-4034	+	+	+	++	tr	+++	102.4°	0
W-5015	0	++	0	++	0	+	—	0
W-5012	0	++	0	0	0	+	—	0
W-4050	0	++	0	0	0	0	—	0
W-4062	0	++	0	0	+	+	—	0
W-4007	+	+	+	+	++	0	—	a
W-4060	+	+	+	+	+	+	—	0
W-5008	+	+	0	0	0	tr	—	0
W-4047	+	+	0	0	0	+	—	0
W-4051	+	+	0	0	0	+	—	0
W-4037	+	+	0	0	tr	+	—	0
W-4026	+	+	0	0	0	0	—	0
W-4028	+	+	0	0	+	+	—	0
W-4055	0	0	+	+	+	++	—	0
W-4086	0	0	+	+	+	+	—	0
W-4068	0	0	+	+	0	0	—	0
W-5005	0	0	+	+	+	0	—	0
W-4013	0	0	0	0	0	0	—	a
Total 22	11	17	9	12	12	15	5	4

[x] 0—Absent + —Present ++—Appearance or
[xx] 0—Absent + —No change increase in severity

*Includes only those patients with fever

† a. Abnormal auriculoventricular conduction
b. Erythema marginatum
c. Pericarditis

tr—Trace

one patient had a persistent aortic diastolic murmur. In the group treated with HPC there were no patients who had diastolic murmurs prior to treatment. During therapy seven patients developed diastolic murmurs; four had basal diastolic, one had a mitral diastolic, and two had both mitral and basal diastolic murmurs. In this group again, all but one patient, who had a persistent aortic diastolic murmur, lost their diastolic murmurs by the end of nine weeks.

Toxic symptoms occurred in sixteen of the thirty-four patients treated with HPC. The most common symptom was diarrhea which was present in fourteen of the sixteen cases. The next most common symptom was abdominal cramping. Nausea and vomiting occurred in a small number of patients. The duration of these toxic symptoms ranged from a few days to a week. In one case mild diarrhea lasted for thirty-eight days. In only one patient did toxic symptoms reach sufficient severity to require supportive therapy. In no case was it necessary to discontinue the drug. Salicylism of some degree occurred in 100 per cent of the patients treated with aspirin. In the majority, symptoms were of moderate severity and it was necessary to stop treatment in only the one instance of hypoprothrombinemia. Tinnitus, loss of hearing, and hyperpnea were the most common symptoms while nausea, vomiting, and epigastric burning occurred with less frequency. The average duration of tinnitus was twenty-two days.

TABLE V. THE PERSISTENCE OR APPEARANCE OF SYMPTOMS AND SIGNS AFTER THERAPY WITH ASPIRIN WAS DISCONTINUED

PATIENT	JOINT MANIFESTATIONS		ABNORMAL ESR		C-REACTIVE PROTEIN		MAXIMUM TEMPERATURE AFTER THERAPY*	OTHER†
	AT THE END OF THERAPY[x]	AFTER THERAPY[xx]	AT THE END OF THERAPY[x]	AFTER THERAPY[xx]	LAST WEEK OF THERAPY	AFTER THERAPY		
W-4044	+	++	+	++	++	+++	105.0°	a, c
W-4020	0	++	0	++	0	++++	103.2°	0
W-4057	0	++	0	++	0	+++	100.4°	b
W-4084	0	++	0	0	0	tr	100.6°	0
W-4052	0	++	0	++	+	++	101.2°	a
W-4065	0	0	0	++	+	+++	101.0°	0
W-5004	0	++	+	++	+	++	—	a
W-4031	0	++	0	0	tr	0	—	0
W-5006	0	++	0	0	tr	0	—	0
W-4040	0	++	+	++	0	+++	—	0
W-5011	0	++	0	0	+	0	—	0
W-4072	0	++	0	0	0	0	—	0
W-4056	0	++	0	0	0	+	—	b
W-4079	0	0	0	++	+	+	—	a
W-4069	0	0	0	++	+	++	—	0
W-4002	0	0	0	0	tr	tr	—	a
W-4074	0	0	0	0	0	+	—	a
W-5014	0	0	0	0	+	++	—	a
Total 18	1	12	3	9	11	14	5	9

[x] 0—Absent +—Present ++—Appearance or
[xx] 0—Absent +—No change increase in severity

*Includes only those patients with fever

† a. Abnormal auriculoventricular conduction
b. Erythema marginatum
c. Pericarditis

tr.—Trace

The persistence, appearance, or reappearance of clinical symptoms and signs or of abnormal laboratory findings after the cessation of therapy are presented in Tables IV and V. The data show no marked difference between the two groups in the number of patients with abnormal clinical or laboratory signs during the posttreatment period of observation. However, at the end of treatment the lesser frequency of joint manifestations and abnormal sedimentation rates among the aspirin-treated patients illustrates the reappearance of these findings in this group in contrast to their persistence in the HPC group. C-reactive protein was demonstrated with equal frequency in both groups, both before and after treatment. The quantity of C-reactive protein present correlated with the severity of the rebound. Absence of this abnormal protein did not preclude the occurrence of a clinical or laboratory relapse after treatment was discontinued. In contrast to the above data, those patients with no evidence of persistence or reappearance of abnormal findings after treatment had no measurable C-reactive protein after cessation of therapy with the following exceptions. In the HPC group one patient had a trace and one had a + reaction; in the aspirin group three patients had traces of C-reactive protein in their sera.

There was little difference between the two groups in the time of reappearance of abnormalities which was usually near the end of the first week following cessation of therapy. There was also little difference in the severity of these relapses. The abnormal findings had usually disappeared by the end of the three weeks' observation period, although abnormal sedimentation rates persisted somewhat longer in a few patients. Retreatment was necessary in only one patient from each group.

Results of the Follow-up Examinations

Follow-up examinations, at monthly intervals for a period of fourteen to seventeen months after the start of treatment, were obtained on thirty-three HPC-treated patients and thirty aspirin-treated patients. Of the five patients who were followed for a shorter time, four were discharged from the service for reasons unrelated to rheumatic fever and one was killed in an accident. None of the patients lost from observation had established murmurs at periods eight to twelve months after the start of treatment except for the one patient who was killed. This latter patient, from the aspirin group, had had a consistent mitral systolic murmur up to eleven months after the start of treatment and pathologic examination of the heart revealed mitral valvulitis.

During the follow-up period monthly cultures revealed that four patients from the HPC group and one patient from the aspirin group acquired a new group A streptococcus different from their original type. An increase in the antistreptolysin titer of their sera occurred in only two of the above patients from whom new group A streptococci were isolated. In addition, there was only one other patient who developed a rise in the antistreptolysin titer during the period of follow-up observations, although the throat cultures had remained negative for beta hemolytic streptococci during this period. Only one patient had clincal evidence of a streptococcal sore throat, and he was treated promptly with penicillin. None of the aforementioned patients had evidence of a clinical relapse or recurrence of rheumatic fever. Of the patients who either acquired a new group A streptococcus or exhibited a rise in their antistreptolysin titer, two, both from the HPC group, had murmurs at the time of their last evaluation. One murmur was considered significant and was present prior to the reacquisition of streptococci. The other was a questionably significant murmur at the final follow-up examination. This latter murmur may have been related to a new streptococcal infection since a mitral systolic murmur heard during the acute illness had been absent for eight months and was again audible two months after a new streptococcus was isolated, although no increase in the patient's antistreptolysin titer was detected.

The occurrence of murmurs in those patients who were followed from fourteen to seventeen months after the start of treatment is presented in Table VI. Fifty per cent of the patients in each group were followed for seventeen months, and eighty per cent were followed for at least fifteen months. At the time of follow-up examination a murmur was considered to be questionably significant by reason of either inconstancy during the period of observation or physical characteristics of the murmur. The former reason was usually the deciding factor in placing a murmur in this category. All patients with murmurs had mitral systolic murmurs. In addition to the mitral murmurs two patients in the HPC group and one patient in the aspirin group had aortic

TABLE VI. THE OCCURRENCE OF MITRAL SYSTOLIC MURMURS FOURTEEN TO SEVENTEEN MONTHS AFTER THE BEGINNING OF THERAPY

	HPC (33 PATIENTS)			ASPIRIN (30 PATIENTS)		
	PREVIOUS HISTORY OF RHEUMATIC FEVER	NO PREVIOUS HISTORY OF RHEUMATIC FEVER	TOTAL	PREVIOUS HISTORY OF RHEUMATIC FEVER	NO PREVIOUS HISTORY OF RHEUMATIC FEVER	TOTAL
Number of patients with:						
Significant murmur	2	8*	10	3†	9	12
Questionably significant murmur	1	3	4	0	2	2
No murmur	4	15	19	4	12	16

*Two of these patients also had aortic diastolic murmurs.

†One patient also had an aortic diastolic murmur and a presystolic apical murmur.

diastolic murmurs, and one patient in the aspirin group had both aortic diastolic and apical presystolic murmurs. There is essentially no difference in the incidence of murmurs between the two groups. In both groups the occurrence of murmurs among the patients whose observed episode of rheumatic fever was a recurrent attack did not differ from the occurrence among those patients with initial attacks. The one patient who was considered to have had pre-existing rheumatic heart disease at the onset of treatment developed no new murmurs.

DISCUSSION

With the dosages employed, aspirin appeared to be more effective than HPC in relieving the signs and symptoms of acute rheumatic fever in the present series of patients. In comparable groups of patients, aspirin treatment resulted in more effective control of joint symptoms, fever, and erythrocyte sedimentation rate than did treatment with HPC. There was no difference between the two drugs in their effect on auriculoventricular block and acute carditis. A fourteen to seventeen month follow-up of the patients likewise revealed no difference between the two groups of patients in the incidence of rheumatic valvular heart disease. The aspirin-treated patients on the whole were more comfortable than the HPC-treated patients even though the toxic symptoms of the drugs were more frequent and severe in the former group. With the exception of the one patient who developed hypoprothrombinemia, the severity of the toxic symptoms of aspirin was not sufficient to outweigh the advantage obtained in the control of the symptoms and signs of the disease.

Blanchard and associates[1] in their original report indicated that the effect of HPC on the fever of acute rheumatic fever was specific and not necessarily related to a nonspecific antipyretic quality of the drug. Maren[5] had observed that the antipyretic effect of cinchoninic acid derivatives was greater than that of aspirin in rats. Although in the present series of patients there is no untreated control group with which to compare the effect of either HPC or aspirin, the rather prompt drop, in the incidence of fever after therapy was started, appears to be directly related to the administration of the drugs. Likewise the return of fever after the discontinuance of therapy appears to have the same relation. Whether or not these relations are the result of either a specific or a nonspecific effect of the drugs cannot be determined from these data.

The pattern of response of arthritis and of the sedimentation rate is more difficult to assess. Certainly in the patients treated with HPC there was not the prompt subsidence of joint findings noted with aspirin. The sharp decline of the curve in Fig. 2 shortly after the start of treatment would indicate that HPC exerted some effect on arthritis. The flattening of the curve at about the ninth day of treatment, the absence of a marked rebound of joint symptoms after therapy, and the gradual decrease in the erythrocyte sedimentation rate with the absence of a rebound would lead one to believe that there may have been little effect in the rheumatic inflammatory process and that the action of HPC was in part analgesic or that the improvement was related to the natural course of the disease. The failure to suppress the joint manifestations completely with HPC may be related to dosage. Simson and Bunim[6] reported good results in the con-

trol of the arthritis of rheumatic fever with HPC. They stated that its action compared favorably with that of aspirin although they had no simultaneously aspirin-treated patients. Their initial dose of HPC was the same as that employed in this study, but if they did not obtain the desired result, they increased the total daily dose to 30 or 40 mgs. per kilogram of body weight. Larger doses of HPC in the present study might have resulted in a response comparable to that observed with the use of aspirin.

During the posttreatment period of observation the number of patients in each group with abnormalities was essentially equal. In general this result was achieved by the recurrence of abnormalities in the aspirin-treated group and the persistence of abnormalities in the HPC-treated group. An exception to this generality was the behavior of the C-reactive protein. C-reactive protein antiserum was not available in a quantity sufficient to permit multiple determinations for its presence during the entire period of observation. Nevertheless, those determinations performed on serum obtained just before cessation of therapy and during the posttreatment period revealed no difference between the two groups. This is in contrast to the behavior of the other indications of rheumatic activity. The absence of C-reactive protein during the last week of therapy gave no assurance that it would not appear later and that the patient would not experience a clinical or laboratory relapse. There was a positive correlation, however, between its presence during the last week of therapy and the persistence or appearance of other abnormalities when treatment was discontinued.

The data obtained during the three weeks posttreatment period appear to indicate that the duration of illness was affected equally by the two drugs or was not affected at all. The same is true for acute carditis and for rheumatic valvular disease during the time the patients were followed.

SUMMARY

The comparative effects of treatment with 3-hydroxy-2-phenylcinchoninic acid (HPC) and aspirin were observed in a study of sixty-eight patients with acute rheumatic fever. One-half, or thirty-four, of the patients received HPC; the remaining one-half were treated with aspirin.

Aspirin exerted a more favorable effect upon arthritis, fever, and erythrocyte sedimentation rate than did HPC. There was no difference between the two treated groups in the course of acute carditis or in the incidence of significant murmurs fourteen to seventeen months after treatment was started. The duration of the acute illness appeared to be equal in the two groups.

In the dosages employed in this study, aspirin appears to be preferable to HPC in the treatment of acute rheumatic fever.

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REFERENCES

1. Blanchard, K. C., Harvey, A. M., Howard, J. E., Kattus, A., Marshall, E. K., Jr., Newman, E. V., and Zubrod, C. G.: The Effect of 3-hydroxy-2-phenylcinchoninic Acid Upon Rheumatic Fever, Bull. Johns Hopkins Hosp. **87**:50, 1950.
2. Marshall, E. K., Jr., Harvey, A. M., Howard, J. E., Blanchard, K. E., Zubrod, C. G., Kattus, A., and Newman, E. V.: The Effect of 3-hydroxy-2-phenylcinchoninic Acid Upon Rheumatic Fever, Trans. A. Am. Phy. **58**:108, 1950.
3. Jones, T. D.: The Diagnosis of Rheumatic Fever, J. A. M. A. **126**:481, 1944.
4. Anderson, H. C., and McCarty, M.: Determination of C-reactive Protein in the Blood as a Measure of the Activity of the Disease Process in Acute Rheumatic Fever, Am. J. Med. **8**:445, 1950.
5. Maren, T. H.: An Estimation of the Antipyretic Activity of Cinchoninic Acid Derivatives, J. Pharmacol. & Exper. Therap. **101**:313, 1951.
6. Simson, J., and Bunim, J. J.: The Anti-rheumatic Effects of 3-hydroxy-2-phenylcinchoninic Acid (HPC) in Gout, Rheumatic Fever and Rheumatoid Arthritis, Am. J. M. Sc. **222**:523, 1951.

INTERRELATIONSHIP OF DIGITALIS AND POTASSIUM IN AURICULAR TACHYCARDIA WITH BLOCK

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AN OVERDOSE of digitalis "can cause practically any form of arrhythmia."[1] Auricular ectopic rhythms, however, have not been shown to occur with any frequency or to manifest any specific form as a consequence of digitalis intoxication. In our experience in patients with advanced congestive heart failure, one form of auricular arrhythmia is a relatively common manifestation of serious digitalis intoxication.[2] On the basis of the electrocardiographic pattern, the abnormal rhythm has been named *paroxysmal auricular tachycardia with block.* The following features have been used to distinguish it from other types of rapid heart action: (1) an auricular rate of 150 to 250 per minute, (2) varying degrees of atrioventricular block, (3) an isoelectric baseline between the P waves, (4) diminution of the atrioventricular delay by exercise, (5) augmentation of the delay by vagal stimulation, and finally (6) a tendency for the tachycardia to persist for days or even months. Thus this arrhythmia exhibits some of the features ascribed to both auricular tachycardia and flutter.[3,4]

It has been shown that changes in body potassium alter the threshold of the heart to the toxic action of digitalis.[5] Ventricular premature beats caused by an excess of digitalis can be stopped by potassium administration.[6,7] Conversely potassium loss, irrespective of how this is achieved, may precipitate digitalis intoxication in patients on maintenance digitalis therapy.[8]

If auricular tachycardia with block is caused by digitalis overdosage, a relationship between this arrhythmia and the potassium balance of the body should be demonstrable. It should be possible to abolish the tachycardia by the administration of potassium and to induce it by depleting body potassium. It is the purpose of this communication to outline such experience gained in the wards of the Peter Bent Brigham Hospital during the past year.

MATERIAL

The patients were divided into three groups.

Group I included six patients, all of whom were digitalized because of congestive heart failure. They experienced fourteen episodes of auricular tachycardia with block. Thirteen of these

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episodes followed either significant increases in digitalis dosage, extensive weight loss after mercurial induced diureses, renal potassium loss, or a combination of these factors. Potassium chloride was administered during ten such attacks in an attempt to control the tachycardia.

Group II comprised two patients with uremia who were receiving digitalis because of left sided heart failure. Auricular tachycardia with block developed during potassium extraction by means of hemodialysis utilizing a Kolff type artificial kidney.*

Group III included five patients with spontaneous auricular ectopic rhythms. Only three received digitalis consisting of small maintenance doses. Four were in congestive heart failure but none had been given mercurial diuretics. Potassium chloride was also administered to these patients in an attempt to restore a normal sinus mechanism.

RESULTS

In all ten instances of paroxysmal auricular tachycardia with block in Group I, potassium was promptly effective in stopping the arrhythmia irrespective of the route of administration (Table I). The reversion of the auricular tachycardia to a normal sinus mechanism was a gradual and sequential process (Fig. 1).

During treatment of auricular tachycardia with block with potassium, there was invariably an initial paradoxical and abrupt increase in the ventricular rate as shown in patient F.G. (Fig. 1, *B*). This was due to a restitution of a 1:1 atrioventricular response which was achieved by a decrease in auricular rate of only 5 to 10 beats per minute. The auricular rate at which a 1:1 ventricular response occurred varied from 148 to 190 beats per minute. The patients frequently complained of palpitation and dyspnea during the transient phase of ventricular acceleration. A continuous diminution of atrioventricular block then took place with apparent forward migration of the P wave. There followed a further decrease in rate until a sinus mechanism was evident. Five of the six patients showed the above sequence. The one exception reverted to auricular fibrillation, the rhythm present prior to the auricular tachycardia with block. The quantity of potassium chloride given varied from 20 to 100 meq. (1.5 to 7.5 Gm.). The earliest electrocardiographic changes were visible within fifteen to thirty minutes after the oral ingestion of the potassium.

The two patients with uremia in Group II had brief periods of hemodialysis against a bath with a reduced potassium concentration. This effected the removal of potassium from the body and was followed by the development of auricular tachycardia with block. Patient E.M. experienced two such episodes. The first developed prior to dialysis after a marked overdose of Digoxin, 2.5 mg. intravenously given over a twelve hour period in addition to a daily maintenance dose of 0.1 Gm. of digitalis leaf. The second attack occurred forty-eight hours later during dialysis, while potassium was being removed. No digitalis had been administered since the first attack. Patient G.J., a 22-year-old woman with lupus erythematosus disseminata, had azotemia and hyperkalemia due to renal shutdown. Because of pulmonary edema, she received 2.0 mg. of Digoxin in divided doses one day prior to dialysis without exhibiting evidence of digitalis intoxica-

*These two patients were studied in cooperation with Dr. John P. Merrill.

tion. Although no additional digitalis was given auricular tachycardia with block occurred during potassium extraction by hemodialysis (Fig. 2). The stages in the evolution of paroxysmal auricular tachycardia with block in these two patients was the reverse of that observed during the elimination of this arrhythmia with potassium. The first change was an increase in the auricular rate at times associated with an alteration in the contour and magnitude but not in the direction of the P wave. Increased atrioventricular block then occurred

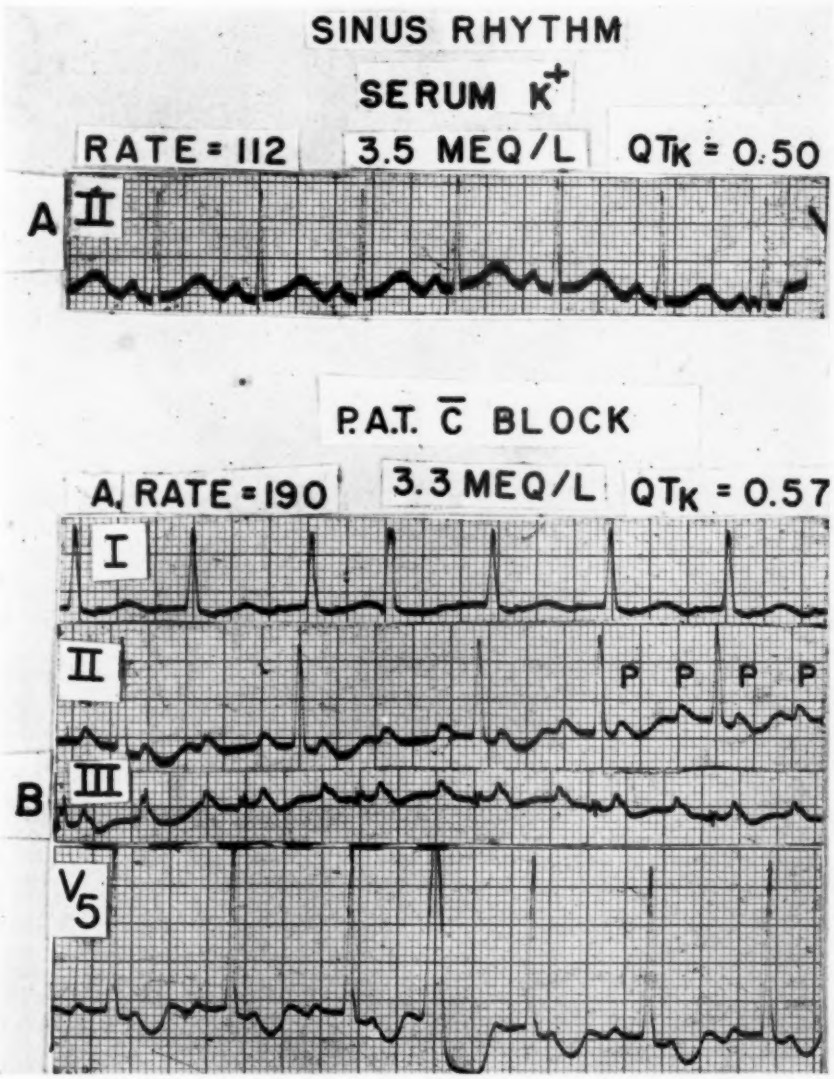

Fig. 1*A*.—F.G., a 48-year-old woman with malignant hypertension and negative potassium balance due to urinary loss. On maintenance digitoxin (0.1 mg. per day). *A*, Hypokalemic curve prior to mercurial. *B*, Auricular tachycardia with block following the diuresis.

as evidenced by apparent migration of the P wave. This was followed by a further acceleration in the auricular rate with concomitant development of 2:1 or greater degree of block.

In patient E.M. the serum potassium level was lowered by 0.8 meq/liter while in patient G.J. the decrease was 2.1 meq/liter; in neither, however, was the serum potassium level subnormal at the time of the inception of the paroxysmal auricular tachycardia with block. Elevating the concentration of bath potassium and thus raising the serum level did not promptly reverse the auricular arrhythmia. About three hours elapsed before normal sinus rhythm was resumed.

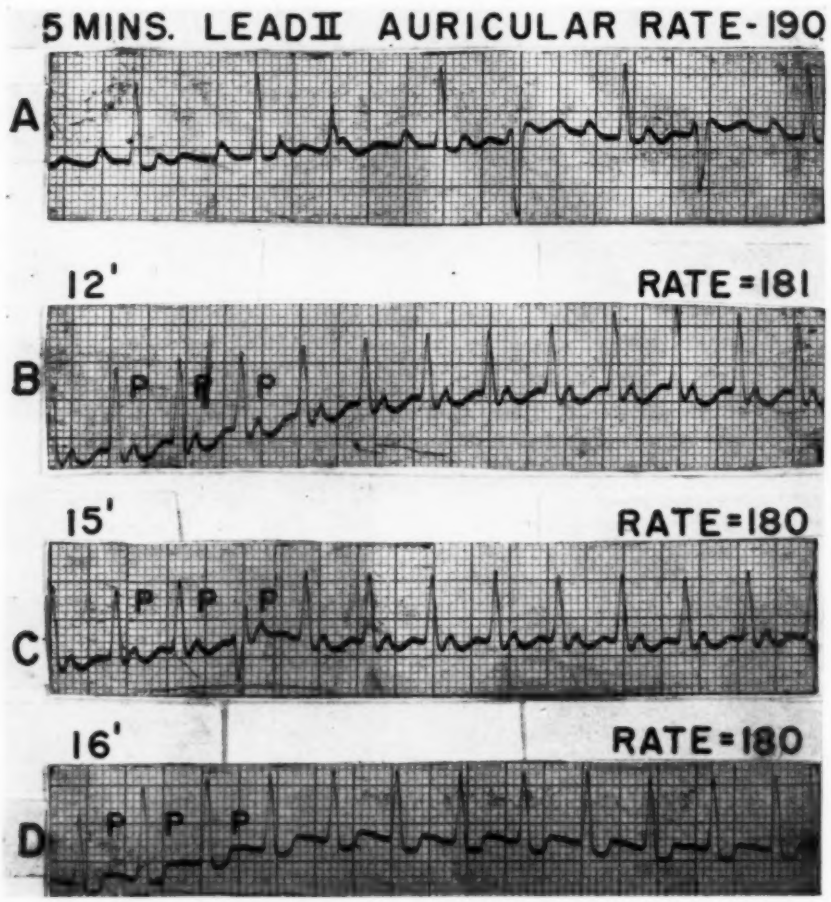

Fig. 1*B*.—F.G. serial tracings after ingestion of 40 meq. of potassium chloride. *A*, Acceleration of ventricular rate due to 1:1 response. *B* to *D*, Apparent forward migration of P wave due to lessening atrioventricular block without change in rate.

Among the five patients in Group III, four had congestive heart failure, while one (J.F.) aside from the presence of auricular tachycardia with block, showed no evidence of heart disease. In none of this group was digitalis implicated in the emergence of the auricular arrhythmia, and potassium administration

did not restore sinus rhythm (Table III). The abnormal auricular mechanisms consisted of auricular tachycardia with block (patients I.W. and J.F.), flutter (patients M.D. and C.S.), and nodal tachycardia (patient A.N.).

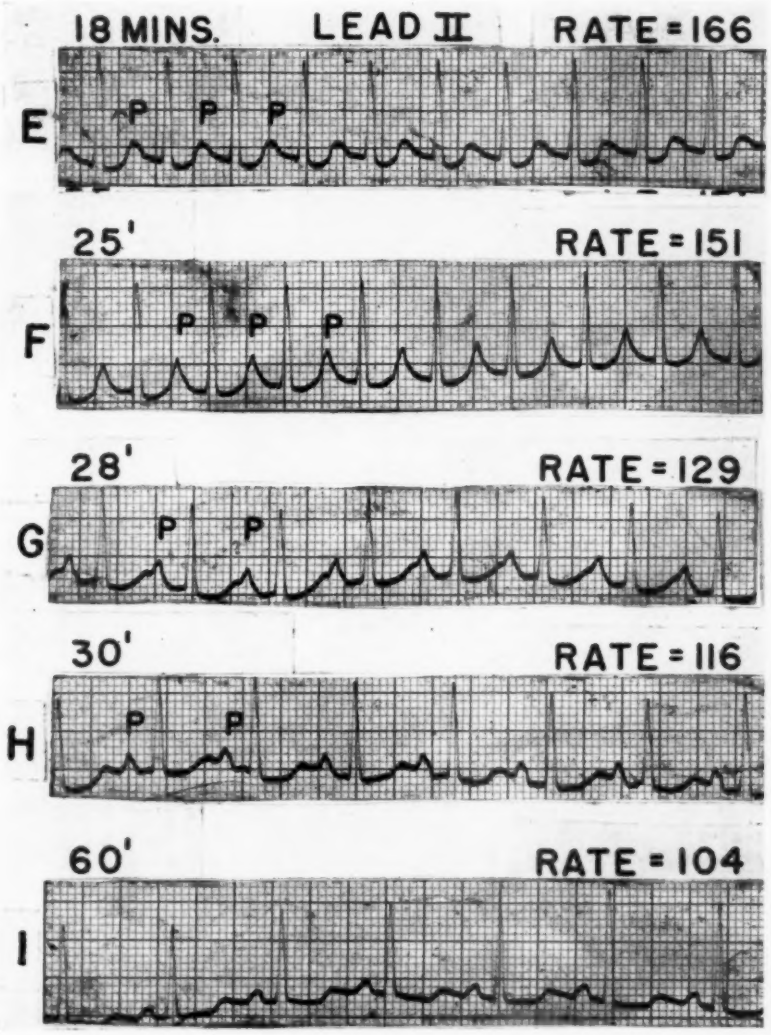

Fig. 1C.—F.G. *E* to *H*, *I*, slowing of auricular rate without change in contour and amplitude of P wave with resumption of normal sinus rhythm. Prior to potassium administration serum level 3.3 meq/liter, one hour after 4.0 meq/liter.

The effect of potassium on the electrocardiogram of two of the patients in this group is shown in Figs. 3 and 4. Patient J.F. was a 14-year-old girl who developed auricular tachycardia with block following a mild upper respiratory infection. Digitalis, quinidine, Pronestyl Hydrochloride, as well as potassium, did not alter the abnormal rhythm (Fig. 3). Patient M.D. was a 72-year-old

TABLE I. ABOLITION OF PAROXYSMAL AURICULAR TACHYCARDIA WITH BLOCK BY POTASSIUM THERAPY (GROUP I)

PATIENT	NO. OF ATTACKS	DIGITALIS			DIURETICS		OTHER PRECIPITATING FACTORS	RHYTHM PRIOR TO AURICULAR TACHYCARDIA WITH BLOCK	POTASSIUM ADMINISTRATION			
		PREPARATION	OVERDOSE	EVIDENCE OF TOXICITY	MERCURIALS	WEIGHT LOSS (Kg.)			ROUTE	AMOUNT (mEq.)	TIME FOR REVERSION (MIN.)	RHYTHM AFTER REVERSION
M. E.	3	Digitoxin and Digoxin	Yes	V.P.B.'s	1. Yes	5	0	N.S.R.	1. 0	0	?	N.S.R.
					2. Yes	1			2. 0	0	?	N.S.R.
					3. No	0			3. Oral	65	45	Sinus Tach.
F. G.	5	Digitoxin	No	Nausea Vomiting Multifocal V.P.B.'s	1. Yes	3	"K+ Losing Nephritis"	N.S.R.	Oral	20-60	30-60	Sinus Tachycardia
					2-5. No	0						
A. B.	2*	Digitoxin	No	0	Yes	5 (5000 c.c. diuresis)	Cortisone	Auricular Fibrillation	Oral	100	120	N.S.R.
E. Q.	1	Digoxin and Ouabain	Yes	First and second degree block V.P.B.'s	No	0	0	N.S.R.	Intravenous	60	45	N.S.R.
C. S.	1	Digitoxin	Yes	Nausea Vomiting Multifocal V.P.B.'s Ventricular Tachycardia	Yes	7.5	0	Auricular Fibrillation	Intravenous	40	90	Auricular Fibrillation
E. G.	2†	Digitalis Leaf and Digitoxin	Yes	V.P.B.'s	No	0	0	N.S.R.	Intravenous	40	120	N.S.R.

V.P.B. = Ventricular premature beats.
N.S.R. = Normal sinus rhythm.
*Second episode of tachycardia was treated with ouabain; ventricular tachycardia and death followed.
†One of the attacks was stopped with procaine amide (Pronestyl Hydrochloride).

TABLE II. INDUCTION OF AURICULAR TACHYCARDIA WITH BLOCK BY POTASSIUM REMOVAL THROUGH HEMODIALYSIS (GROUP II)

†One of the attacks was stopped with procaine amide (Pronestyl Hydrochloride).

TABLE II. INDUCTION OF AURICULAR TACHYCARDIA WITH BLOCK BY POTASSIUM REMOVAL THROUGH HEMODIALYSIS (GROUP II)

PATIENT	NO. OF EPISODES	DIGITALIS PREPARATION	POTASSIUM EXTRACTION				OTHER EVIDENCE OF DIGITALIS INTOXICATION	AURICULAR TACHYCARDIA WITH BLOCK STOPPED BY—
			BATH POTASSIUM CONCENTRATION (meq/liter)	DURATION OF EXTRACTION	SERUM POTASSIUM (meq/liter)			
					PRIOR TO DIALYSIS	AT ONSET OF ARRHYTHMIA		
E. M.	2*	Digitalis leaf and Digoxin	2.0	30 min.	4.7	3.9	Nausea and vomiting; ventricular premature beats Ventricular tachycardia	Discontinuation of dialysis
G. J.	1	Digoxin	2.5	60 min.	7.7	5.6	0	Discontinuation of dialysis

*One of the episodes caused by an overdose of Digoxin.

TABLE III. POTASSIUM ADMINISTRATION IN CASES WITH AURICULAR ARRHYTHMIAS IN WHICH DIGITALIS THERAPY WAS NOT A CAUSATIVE FACTOR (GROUP III)

PATIENT	NO. OF EPISODES	DIGITALIS		DIURETICS	TYPE OF ARRHYTHMIA	POTASSIUM ADMINISTRATION		
		PREPARATION	OVERDOSE OR TOXICITY			ROUTE	AMOUNT (meq)	RESULT
I. W.	1	0	0	0	Auricular tachycardia with block	Oral	200	Unaltered
J. F.	1	0	0	0	Auricular tachycardia with block	Oral	100	Unaltered
M. D.	2*	Digitalis leaf	0	0	Auricular flutter	Oral	100	Unaltered, severe hyperkalemia
C. S.	1*	Digoxin	0	0	Auricular flutter	Intravenous	60	Unaltered
A. N.	1	Digoxin	0	0	Nodal tachycardia	Intravenous	40	Unaltered, severe hyperkalemia

*Episodes controlled or reverted to sinus rhythm by increased digitalis therapy.

man with coronary artery disease and left ventricular heart failure but without renal impairment. He experienced two attacks of auricular flutter. The first was controlled by digitalization and the second occurred while on maintenance digitalis. He was given 100 meq. (7.5 Gm.) of potassium chloride orally in an attempt to revert this second episode of flutter. Within an hour after the ingestion of potassium salt severe hyperkalemia developed with brief intervals of cardiac standstill. The hyperkalemia was reversed with hypertonic saline. Notwithstanding the advanced potassium intoxication, the flutter continued (Fig. 4).

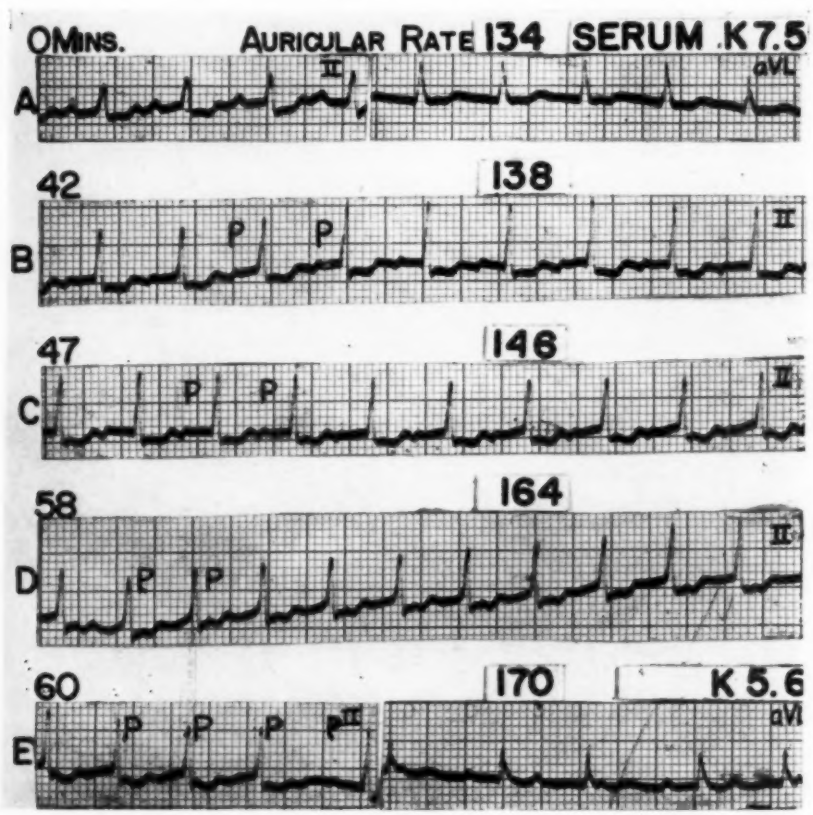

Fig. 2.—G.J., 22-year-old woman with uremia. Dialyzed against a bath with potassium concentration of 2.5 meq/liter. *B*, Change in P wave with increased rate heralding onset of auricular tachycardia forty-two minutes after start of dialysis. *B* to *D*, Backward migration of P wave with increasing rate. *E*, Emergence of 2:1 heart block after one hour of dialysis.

DISCUSSION

This study indicates that in certain patients with congestive heart failure an overdose of digitalis may initiate paroxysmal auricular tachycardia with block. Recently we have produced this same arrhythmia in dogs by a large overdose of

acetyl strophanthidin,* an ultrarapidly acting strophanthin derivative (Fig. 5). In man as well as in dogs the appearance of auricular tachycardia with block augurs possible ventricular tachycardia. The continued administration of digitalis in the presence of auricular tachycardia with block, which develops after an increased dose of digitalis or a mercurial induced diuresis, may precipitate severe digitalis poisoning or even death. Notwithstanding the serious hazard of digitalis under these circumstances, the practice has been to give more digitalis rather than to discontinue it. The basis for such practice is the widespread lack of recognition of the common etiologic role of digitalis in the genesis of this arrhythmia.

At times the very presence of auricular tachycardia with block goes undetected due to its resemblance to auricular fibrillation. On auscultation the heart beat may be rapid and irregular. Electrocardiographic differentiation may be difficult because of the presence of one or all of the following features: (1)

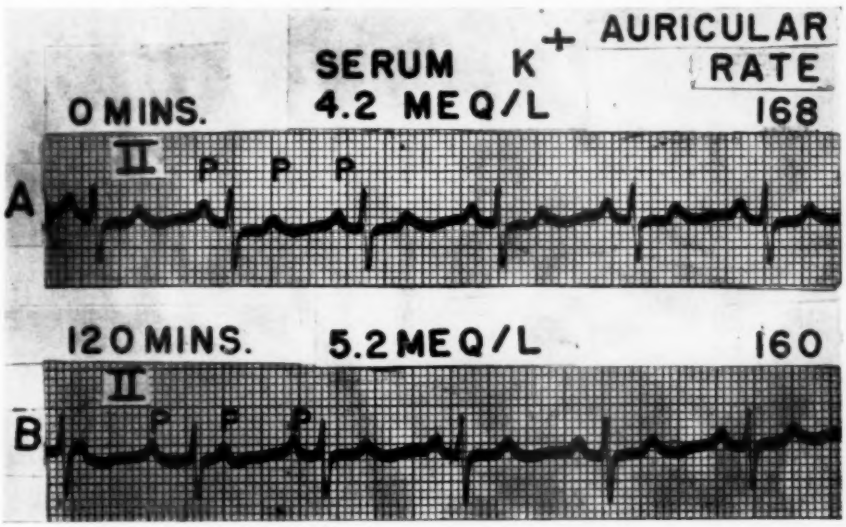

Fig. 3.—J.F., 14-year-old girl without heart disease but with auricular tachycardia with block continuous for eight months. *A*, Prior to oral ingestion of 100 meq. of potassium chloride. *B*, Two hours after the potassium. No change in mechanism, slight slowing in rate.

changing degrees of atrioventricular block in consecutive complexes, (2) absence of an arithmetic ratio between auricular and ventricular response as is true in most cases of flutter, (3) diminutive P waves, and (4) a rapid ventricular rate. In patients with established auricular fibrillation, acceleration and regularization of ventricular response following manipulation of digitalis dosage or changes in electrolyte balance should raise suspicion of the presence of auricular tachycardia with block. When the routine electrocardiogram does not show such an auricular mechanism, exploration of the precordium with CR leads may reveal the blocked P waves. Proper therapy consists of stopping digitalis and the judicious use of one of the salts of potassium administered with continuous electrocardiographic supervision.

*Made available through the courtesy of Dr. B. L. Martz, Eli Lilly & Company.

Digitalis intoxication is not the sole condition which predisposes to paroxysmal auricular tachycardia with block. In a patient reported by Schwartz and Levine[9] the arrhythmia persisted almost continuously for twenty-five years without digitalis being at any time implicated. In two cases cited here, factors other than digitalis initiated the arrhythmia. In most cases, however, digitalis appears to be causally related. This is born out by the experience of Decherd, Herrmann, and Schwab.[4] In twenty-two of forty cases of paroxysmal auricular tachycardia with block, distinct digitalis overdosage was associated with the onset of the arrhythmia. At the Peter Bent Brigham Hospital forty of fifty instances of auricular tachycardia with block exhibited evidence of digitalis intoxication, and in one-third of the cases significant diureses preceded the onset of the tachycardia.[2]

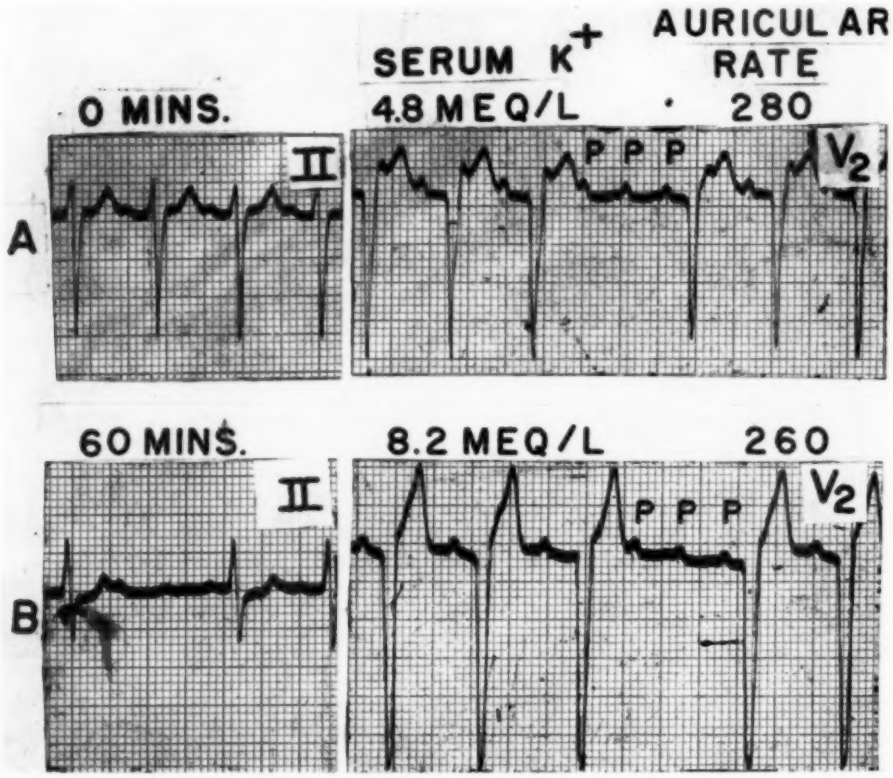

Fig. 4.—M.D., man aged 72 with old antero-septal myocardial infarction and auricular flutter, no digitalis. *A*, Control. *B*, One hour after 100 meq. of potassium chloride orally, severe hyperkalemia, with persistence of arrhythmia.

This study further demonstrates that enhancement of the toxic action of digitalis accompanying depletion of body potassium affects auricles as well as ventricles. In four digitalized patients (F.G., A.B., Table I, and E.M., G.J., Table II) potassium loss without additional digitalis was adequate to produce auricular tachycardia with block. The potassium loss produced by mercurial

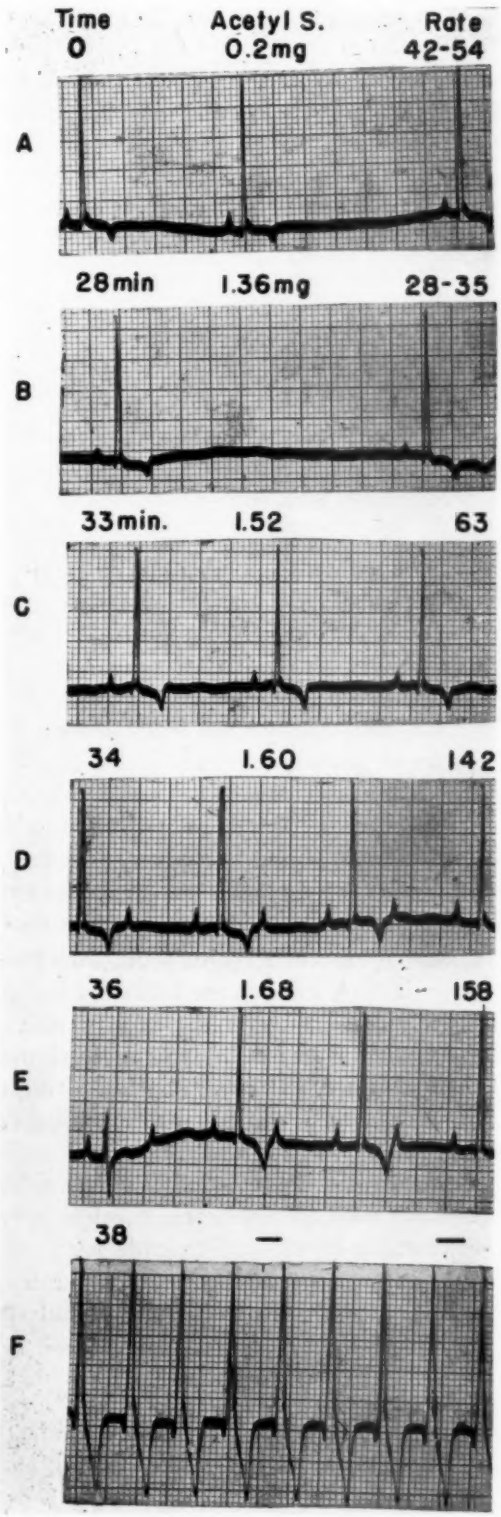

Fig. 5.—Auricular tachycardia with block produced in dog by an overdosage of acetyl strophanthidin. *A*, Sinus arrhythmia prior to digitalis body. *B*, Bradycardia induced by digitalis action. *D* and *E*, Auricular tachycardia with 2:1 block. *F*, Ventricular tachycardia without additional Acetyl Strophanthidin.

diuresis may be of sufficient magnitude to lower the auricular threshold to such an action of digitalis. If potassium removal in the digitalized patient is a critical factor, then the sequence in the evolution of this arrhythmia should mirror the converse process, namely that of the restitution of a normal auricular mechanism by the action of potassium. This indeed was the case. In the development and recession of auricular tachycardia with block identical electrocardiographic phases were observed though these proceeded in opposite directions.

The manner in which potassium acts on the digitalized heart in the development and abolition of auricular tachycardia with block is unknown. Whether the action is through the restitution or production of cellular deficits or by a nonspecific pharmacologic effect resulting from elevation or lowering of extracellular concentrations is uncertain. Two facts at hand suggest that the action is at the cellular level. First, a significant lowering of the serum potassium concentration occurred in only one of the six patients at the time of the onset of the auricular arrhythmia. Second, in the two patients in whom potassium was removed through dialysis, restoration of a ighh serum level did not promptly reverse the tachycardia.

Potassium has not been shown to abolish auricular arrhythmias other than auricular tachycardia with block. In the latter, a background of digitalis intoxication is a prerequisite for its effective action. When potassium restores a normal rhythm, its earliest effect consists of a slowing of the auricular rate. This is apparent after the administration of 20 to 40 meq. If no such slowing is evident, it is unlikely that more potassium will induce any change. The administration of large doses of potassium to obviate digitalis intoxication is hazardous.[10] "In effect one leaps from the frying pan of digitalis intoxication into the fire of potassium poisoning."[11] When potassium is being given to patients with advanced congestive heart failure, frequent electrocardiograms are indicated. The development of tent-shaped T waves is one of the earliest evidences of hyperkalemia. In its presence potassium medication should be discontinued.

In summary, paroxysmal auricular tachycardia with block is a frequent and distinct entity. In the digitalized patient the following features in our experience help in its recognition: (1) It is an auricular tachycardia with a rate ranging from 150-190, (2) the patients who exhibit this arrhythmia are suffering from advanced congestive heart failure, (3) manipulation of digitalis dosage or mercurial induced diuresis is the most common precipitating condition, (4) in the cases studied the onset and termination of the tachycardia were gradual and sequential, (5) the electrocardiogram revealed P waves which were usually upright in Leads I, II, and III with an isoelectric baseline between these auricular waves, (6) the atrioventricular block was variable with frequent Wenckebach-like phenomena, (7) ventricular premature beats were common. This arrhythmia has the same grave significance as ventricular bigeminal rhythm.

CONCLUSIONS

1. In a group of six patients with congestive heart failure, digitalis intoxication was associated with the onset of paroxysmal auricular tachycardia with

block. This arrhythmia could be terminated by oral or intravenous administration of potassium salts.

2. In two digitalized patients with uremia, the extraction of potassium by means of hemodialysis was associated with the development of auricular tachycardia with block.

3. In five patients with varying auricular ectopic mechanisms, but in whom digitalis intoxication was absent, potassium administration was without effect.

4. In most instances, paroxysmal auricular tachycardia with block is an auricular manifestation of digitalis intoxication.

5. It seems probable that potassium depletion sensitizes the auricle to the toxic action of digitalis.

REFERENCES

1. Katz, L. N.: Electrocardiography, Philadelphia, 1946, Lea & Febiger.
2. Wyatt, N., Lown, B., and Levine, H. D.: In preparation.
3. Barker, P. S., Wilson, F. N., Johnston, F. D., and Wishart, S. W.: Auricular Paroxysmal Tachycardia With Auriculoventricular Block, Am. Heart J. **25**:765, 1943.
4. Decherd, G. M., Herrmann, E. H., and Schwab, E. H.: Paroxysmal Superventricular Tachycardia With Auriculoventricular Block, Am. Heart J. **26**:446, 1943.
5. Lown, B., Weller, J. M., Wyatt, N., Hoigne, R., and Merrill, J. P.: Effects of Alterations of Body Potassium on Digitalis Toxicity, J. Clin. Investigation **31**:648, 1952.
6. Sampson, J. J., and Anderson, E. M.: The Treatment of Certain Cardiac Arrhythmias With Potassium Salts, J. A. M. A. **99**:2257, 1932.
7. Enselberg, C. C., Simmons, H. G., and Mintz, A. A.: The Effects of Potassium Upon the Heart With Special Reference to the Possibility of Treatment of Toxic Arrhythmias Due to Digitalis, Am. Heart J. **39**:713, 1950.
8. Lown, B., Saltzberg, H., Enselberg, C. D., and Weston, R. E.: Interrelation Between Potassium Metabolism and Digitalis Toxicity in Heart Failure, Proc. Soc. Exper. Biol. & Med. **76**:797, 1951.
9. Schwartz, W. B., and Levine, S. A.: A Case of Paroxysmal Auricular Tachycardia With Block Present Almost Continuously for Twenty-Five Years, Circulation **1**:936, 1950.
10. Brown, H., Tanner, G. L., and Hecht, H. H.: The Effect of Potassium Salts in Subjects With Heart Disease, J. Lab. & Clin. Med. **37**:506, 1951.
11. Levine, H. D., Vazifdar, J. P., Lown, B., and Merrill, J. P.: "Tent-shaped" T Waves of Normal Amplitude in Potassium Intoxication, Am. Heart J. **43**:437, 1952.

THE CLINICAL RESULTS OF ORAL AND PARENTERAL ADMINISTRATION OF 2-(N′p-TOLYL-N′-m-HYDROXYPHENYLAMINOMETHYL) IMIDAZOLINE HYDROCHLORIDE (REGITINE) IN THE TREATMENT OF HYPERTENSION AND AN EVALUATION OF THE CEREBRAL HEMODYNAMIC EFFECTS

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THE CLOSE association between the autonomic nervous system and the arterial blood pressure has stimulated a great deal of interest in the study of various adrenergic blocking agents for the treatment of hypertension. Regitine,* or 2-(N′-p-tolyl-N′-m-hydroxyphenylaminomethyl) imidazoline hydrochloride, is the hydrochloride salt of an imidazoline compound related to Priscoline. It has been found to have marked epinephrine and adrenergic blocking properties[1,2,3] and was therefore investigated as a potential hypotensive agent in the treatment of patients with essential hypertension.[4] The following study is an evaluation of the drug when used for this purpose. In addition, cerebral blood flow determinations were done on six patients with hypertension before and after reduction in blood pressure with this drug.

METHODS

Clinical studies.—There were forty-eight patients in this series, all of whom had hypertension. There were six white men, fifteen white women, ten Negro men, and seventeen Negro women. Three of the patients were in the third decade, six in the fourth decade, thirty in the fifth decade, six in the sixth decade, and three in the seventh decade of life. All were treated as outpatients. The control studies consisted of semiweekly visits to the clinic for one-to-three months. During this time, routine urinalyses, determinations of blood urea nitrogen, electrocardiograms, routine blood examinations, intravenous pyelograms, phenolsulfonphthalein determinations, and urea clearance studies were done. The blood pressures were taken in the supine and upright positions on each visit to the clinic during the control periods, as well as during the periods of drug administration. After the control studies were completed, sixteen of the forty-eight patients were given 1 to 2 mg./kg. of Regitine intravenously in order to evaluate responsiveness

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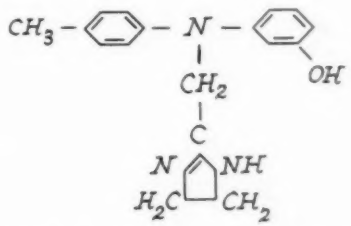
to the drug. Subsequent to the injections, the blood pressures, pulse rates, and subjective sensations were observed for three hours or more on each patient. The intravenous administration was repeated five times at semiweekly intervals. Intravenous medication was not attempted on a prolonged basis. After this initial study, four patients were lost from the clinic. The remaining twelve were placed on the oral form of the drug. They were started on a dose of 50 mg. every six hours. The amount of drug per dose was gradually increased until a significant reduction in blood pressure occurred or until side reactions forced discontinuance of the drug. The maximum tolerated dose varied between 100 and 900 mg. in twenty-four hours. Thirty-two of the original forty-eight patients were given the drug by the intramuscular route (1 mg./kg.) This was repeated daily for four days, and all observations were recorded. After this period, four patients were lost from the clinic. Sixteen of the remaining twenty-eight patients were continued on intramuscular therapy for three months or more, and the other twelve were started on the oral form of the drug. Those patients who continued to take the drug intramuscularly received it twice a day if they were capable of administering it to themselves, but those who had to return to the clinic for their injections received it only once a day. Placebos were substituted in those patients showing any objective response in an attempt to minimize psychogenic factors. Laboratory studies were repeated every four to six weeks or more frequently if indicated.



2-(N′-p-tolyl-N′-m-hydroxyphenylaminomethyl) imidazoline hydrochloride

Fig. 1.—Chemical structure of Regitine.

Cerebral blood flow studies.—Cerebral oxygen consumption and cerebral blood flow were determined by the nitrous oxide method.[5] Control determinations were completed following which 1.0 mg./kg. of Regitine was given intramuscularly. Forty minutes later the cerebral blood flow was again determined. Techniques for blood gas analysis are those previously described.[5] Blood pressure was determined by a damped mercury manometer.

RESULTS

Clinical studies.—The typical blood pressure response to the intravenous administration of Regitine in a patient with hypertension is shown in Fig. 2. There is a blocking of the vasopressor effect of norepinephrine administered one

hour after the use of Regitine. The reduction in blood pressure was greatly augmented in the standing position; therefore, a marked postural reduction in blood pressure occurred in all patients in whom the drug was administered by the intravenous route (Table I). The blood pressure reduction lasted one to ten hours after the administration of the drug, but most commonly, the maximum effect was lost after two to three hours. Frequently, an orthostatic response could be elicited for several hours after there was no discernible supine response (Fig. 2). The values presented in Table I are the averages of five days of drug administration for each individual patient. Percentagewise, the mean diastolic and the systolic blood pressures for the group decreased to about the same degree, with an 18 per cent fall in systolic pressure and a 22 per cent fall in diastolic pressure with the patients supine. This represents a greater fall in systolic than in diastolic blood pressure when expressed in mm. Hg, namely, 38 mm. and 26 mm., respectively. Both the systolic and diastolic blood pressures decreased about twice as much in the upright position, 45 and 44 per cent, respectively. Tachycardia was usually associated with the hypotensive response. The pulse volume decreased, probably indicating decreased cardiac stroke volume. A summary of the results obtained following various routes of drug administration are presented in Table II.

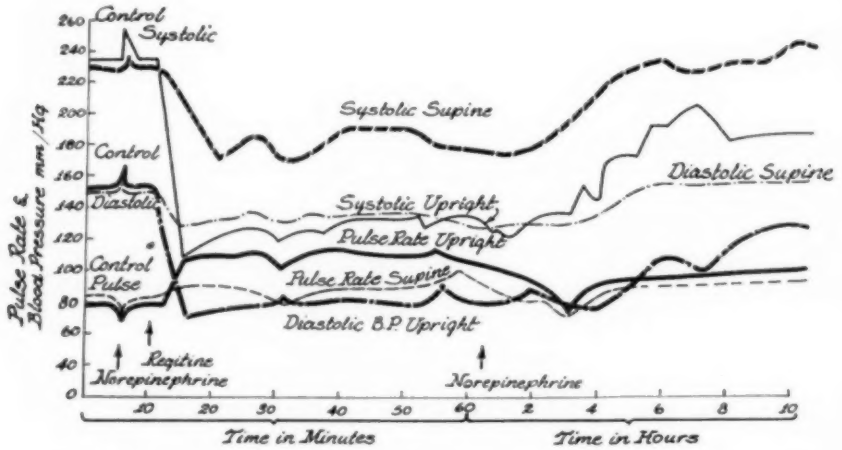


Fig. 2.—Typical blood pressure response to intravenous Regitine (1 mg./kg. I.V.) in a patient with essential hypertension. There is an immediate drop in both systolic and diastolic blood pressure which is predominantly an orthostatic effect. After three hours the supine blood pressure returned to the control levels, but when the patient stood up the blood pressure continued to be lower than control values. Tachycardia was associated with the orthostatic hypotensive effect of the drug. After Regitine, there was no pressor response to norepinephrine (0.1 mg. I.V.).

In Table III are shown the side effects encountered when Regitine was given intravenously. None of these symptoms was severe enough to be an absolute contraindication to the use of the drug, although four patients refused to submit themselves to continued therapy. In addition to the side reactions noted in Table III, one patient developed an electrocardiographic pattern of multifocal premature ventricular contractions, but after thirty minutes normal sinus rhythm

TABLE I. BLOOD PRESSURE RESPONSE TO INTRAVENOUS REGITINE*

PATIENT	RACE	SEX	AGE (YR.)	DOSE mg./kg.	CONTROL B. P. (SYS./DIAST.)		LOWEST B. P. (SYS./DIAST.)		% OF CONTROL (SYS./DIAST.)	
					SUPINE	ERECT	SUPINE	ERECT	SUPINE	ERECT
1.	N.	F.	45	1	200/108	210/118	158/80	90/40	79/74	43/34
2.	W.	M.	29	1	166/106	166/106	154/110	120/80	93/104	72/76
3.	W.	F.	47	2	204/120	194/120	200/110	130/75	98/92	67/63
4.	N.	F.	44	1	208/116	220/140	186/88	88/68	90/76	40/49
5.	N.	F.	48	1	180/106	184/120	176/74	126/62	98/70	69/52
6.	N.	F.	49	1	196/126	204/138	188/120	112/94	96/95	55/68
7.	N.	F.	34	2	256/128	258/130	210/100	130/68	82/78	50/52
8.	N.	F.	63	1	196/110	200/115	136/76	152/84	69/69	76/73
9.	N.	F.	42	1	260/180	250/200	150/106	90/60	58/59	36/30
10.	N.	F.	47	1	192/112	208/128	160/104	120/90	83/93	58/70
11.	W.	F.	47	2	200/112	192/116	130/88	70/54	65/79	36/47
12.	N.	F.	35	1	152/104	178/130	120/60	140/80	79/58	79/62
13.	W.	F.	50	3	185/96	169/100	158/98	80/60	85/102	47/60
14.	W.	M.	46	1	234/150	238/154	208/128	110/70	89/85	46/45
15.	W.	F.	45	1	166/112	144/100	138/60	60/50	83/54	42/50
16.	W.	F.	54	1	210/124	218/146	122/82	138/86	58/66	63/59
Mean				1.3	200/119	202/129	162/93	110/70	82/78	55/56

*Averages of five days of Drug Administration.

W = white; N = Negro; M = male; F = female. B.P. = blood pressure.

TABLE II. COMPARISON OF THERAPEUTIC RESPONSE TO REGITINE BY DIFFERENT ROUTES OF ADMINISTRATION—EXPRESSED AS MEAN VALUES

ROUTE OF ADMIN.	POSITION	CONTROL BLOOD PRESSURE	ACUTE RESPONSE LOWEST BLOOD PRESSURE		RESPONSE AFTER THREE MONTHS	
			mm. Hg	% OF CONTROL S/D*	NO. RESPONDING[1]	MBP FOR GROUP
I. V.	Supine	200/119	162/93	81/78	—	—
16 patients	Upright	202/129	110/70	55/54	—	—
I. M.	Supine	205/123	174/100	85/81	4	190/112[2]
32 patients[2]	Upright	202/134	122/86	60/64	6[3]	180/106[2]
Oral	Supine	195/115	185/108[4]	95/94	None[4]	200/118[5]
24 patients	Upright	198/118	170/100	86/85	None	202/121

*Average percentile change.

[1]Decrease of more than 40 systolic and 20 diastolic, or a decrease of absolute values to 150/100 (upright) or below.

[2]Only sixteen of the thirty-two patients were placed on long term therapy (three months).

[3]Includes the same four patients that showed a continued supine response.

[4]Only six of the twenty-four patients showed a significant reduction in blood pressure initially (more than 20 mm./Hg diastolic).

[5]The drug was discontinued in all but six of the twenty-four patients because of severe gastrointestinal manifestations.

returned. Otherwise, there were no changes noted in the electrocardiograms of these patients. Another patient with a history of angina pectoris experienced mild substernal pain following intravenous and intramuscular injections, probably the result of the reduction in blood pressure and simultaneous reflex tachycardia. There were no associated electrocardiographic changes. Only two patients of the sixteen had no symptoms at all. Five of the patients had a postural hypotension of sufficient severity so that they were unable to stand immediately after receiving the drug, and they had to remain supine for one to two hours. Relief of symptoms associated with the hypertension also occurred, particularly encephalopathic manifestations. In one patient with severe intractable suboccipital headache and visual disturbances considered to be of an encephalopathic origin (Grade 4 eyegrounds), there was immediate relief of symptoms with the reduction in blood pressure. After five days of intravenous therapy the patient was given the drug by mouth but could not tolerate it by this route; therefore, she was again started on intravenous Regitine. Continued administration of the drug produced less and less reduction in blood pressure and at the same time less symptomatic relief until finally (after five weeks) no relief at all was obtained.

TABLE III. SIDE EFFECTS NOTED IN PATIENTS TREATED WITH REGITINE BY DIFFERENT ROUTES OF ADMINISTRATION[1]

SYMPTOM	INTRAVENOUS[2]		INTRAMUSCULAR[3]		ORAL[4]		SYMPTOM	INTRAVENOUS[2]		INTRAMUSCULAR[3]		ORAL[4]	
	NO.	%	NO.	%	NO.	%		NO.	%	NO.	%	NO.	%
None	2	13	8	25	6	25	Dizziness (supine)	4	25	3	9	2	8
Tachycardia and/or palpitation	13	81	19	59	4	17	Dizziness (upright)	7	44	12	38	1	4
"Hot Flush"	13	81	—	—	—	—	Somnolence	3	19	2	6	—	—
"Stuffy" nose	7	44	18	56	4	17	Hyperpnea	2	13	—	—	—	—
Nausea	6	38	3	9	6	25	Tinnitus	1	6	—	—	—	—
Weakness	5	31	14	44	6	25	Diarrhea	—	—	7	22	18	75
Diaphoresis	5	31	3	9	—	—	Vomiting	—	—	2	6	4	17

[1]Intravenous and intramuscular routes, 1 to 2 mg./kg. and oral route 100 to 900 mg. daily depending on response or side reactions.
[2]Sixteen patients.
[3]Thirty-two patients—short term study. Only sixteen were continued for three months.
[4]Twenty-four patients—initial side reactions.

A summary of the results following the intramuscular administration of the drug is presented in Table II and the side effects in Table III. In the acute studies, there was a significant decrease in blood pressure in twenty-nine of the thirty-two patients. This was most marked in the upright position and was about equivalent to the decrease following intravenous administration of the drug. However, the orthostatic effect and tachycardia were less marked; the onset of action was less rapid; and the drug was effective for a longer period (usually three to four hours but twelve to eighteen hours in several instances).

Those patients with severe hypertensive headaches experienced complete relief during the hypotensive response to the drug. Of the sixteen patients who continued on intramuscular therapy for prolonged periods, two patients had associated cardiac failure. Both of them showed improvement with no change in management other than the reduction of the blood pressure. All of the sixteen patients in this group obtained an initial reduction in blood pressure. However, as the patients continued on the drug, increasing amounts were needed to produce a response equivalent to the initial one, and after three months, all but six (38 per cent) of the patients were refractory to the drug. These six patients developed a partial refractoriness and required 5 to 6 mg./kg. to obtain a hypotensive response equivalent to the initial one. Two of these patients have continued to administer the drug to themselves twice a day for the past nine months, and when taken in the upright position the blood pressure has remained within normal limits. Initially, one of these presented Grade 4 eyegrounds, but the hemorrhages and papilledema subsided as the pressure remained lowered. Upon placebo administration in these two patients the previous hypertensive levels quickly recurred, despite the prolonged period of drug administration.

The results following oral therapy were less encouraging than those following the parenteral administration of the drug. Because of severe gastrointestinal symptoms, the dose of the drug could not be increased to a level which would reduce the blood pressure in one-half of the twenty-four patients. These twelve patients had severe diarrhea and cramping abdominal pain, while four also had nausea and vomiting. Concurrent administration of Amphojel was tried as a method of decreasing gastrointestinal irritability but was ineffective. Of the remaining twelve patients, six had milder symptoms of nausea, diarrhea, and/or weakness, and six had no distressing symptoms. These latter six patients had a temporary but definite postural reduction in their blood pressure but became refractory to the drug. None of them obtained a long term decrease in blood pressure without developing prohibitive gastrointestinal symptoms. In the six patients who initially experienced mild side reactions the results were equivocal, the fall in pressure being too small to be considered significant. Any reduction in blood pressure could usually be duplicated by placebos. Further reduction in blood pressure was attempted in these six patients by increasing the dose of Regitine but prohibitive gastrointestinal manifestations occurred. There was no evidence of renal damage associated with prolonged administration of the drug, either by the oral or the intramuscular routes.

Cerebral blood flow studies.—Associated with a significant reduction in blood pressure there was a proportional reduction in cerebrovascular resistance. As a result, cerebral blood flow was maintained. There were no alterations in the partial pressure of carbon dioxide or in oxygen consumption by the brain.

DISCUSSION

One may conclude from the present study that in most patients (94 per cent of this series) with hypertension, parenteral administration of Regitine is effective in reducing the blood pressure, particularly in the upright position. Therefore,

TABLE IV. EFFECT OF REGITINE ON CEREBROVASCULAR HEMODYNAMICS AND CEREBRAL OXYGEN CONSUMPTION

PATIENT	MBP		CBF		$CMRO_2$		CVR		$APCO_2$	
	C*	D†	C	D	C	D	C	D	C	D
1	135	108	46	50	4.2	3.7	2.9	2.2	38	37
2	146	120	62	61	4.0	3.9	2.4	2.0	39	40
3	149	142	43	48	3.2	2.6	3.5	2.9	43	40
4	156	137	54	65	1.9	2.0	2.9	2.1	40	42
5	130	86	55	49	2.0	3.1	2.4	1.8	40	44
6	138	96	57	48	3.6	3.8	2.4	2.0	35	38
Mean	142	115	53	53	3.2	3.2	2.8	2.2	39	40

MBP = Mean blood pressure = diastolic plus pulse pressure/3.
CBF = Cerebral blood flow, c.c./100 Gm. brain/min.
$CMRO_2$ = Oxygen uptake per 100 Gm. brain/min.
CVR = Cerebrovascular resistance, $\frac{MBP.}{CBF}$
$APCO_2$ = Arterial partial pressure of CO_2.
*C = Control.
†D = Forty minutes after Regitine (1 mg./kg.).

this drug is of value in the temporary relief of hypertensive crises and as interval therapy between courses of more effective therapeutic agents. The use of Regitine is seriously limited by the development of a refractory state, and the fact that the decrease in blood pressure is predominantly orthostatic. Adequate reduction in blood pressure may be hard to achieve in many seriously ill and bedfast patients since most of them will remain in the supine position. The use of the oral preparation is of little value in the treatment of hypertension because of the high incidence of gastrointestinal disturbances. In the present series, there was not sufficient benefit in any of the patients treated with the drug when administered orally to justify advocacy of its use. This does not indicate that the drug when used orally is of no value in conditions wherein less complete adrenergic blockade is necessary to produce the desired therapeutic responses, such as peripheral vascular disease and in the preoperative management of patients with pheochromocytomas. The authors have observed two adults and one child with fixed hypertension due to pheochromocytomas. The blood pressure was maintained within normotensive ranges with the oral drug in one of the adults and in the child prior to operation. Gastrointestinal side reactions prohibited an adequate dose to be administered to reduce effectively the blood pressure in the second adult.

The fact that cerebral blood flow was maintained despite a reduction in blood pressure is consistent with observations on other hypotensive drugs.[7,8] The cerebral circulation appears to be able to compensate for the reduction in blood pressure by decreasing the cerebrovascular resistance enough to maintain cerebral blood flow. The cerebral vasodilatation is probably not a result of adrenergic blockade since a similar dilatation takes place after reduction in blood pressure with Veriloid, which apparently does not produce peripheral blockade of

the sympathetic nervous system. Kety and Schmidt[9] have suggested that adjustments of cerebrovascular hemodynamics are such that the partial pressures of oxygen and carbon dioxide tend to remain constant. The current observations support this concept. It is quite obvious that despite the existence of a rather severe hypertensive state in these patients, the cerebral vessels are able to dilate in much the same manner as do the cerebral vessels in normotensive individuals following blood pressure reduction.

CONCLUSIONS

1. The use of Regitine 2-(N′-p-tolyl-N′-m-hydroxyphenylaminomethyl) imidazoline hydrochloride for the treatment of hypertension has been evaluated. The drug was given intravenously to sixteen patients and intramuscularly to thirty-two patients for short periods of time. Following the acute studies, sixteen patients were placed on the parenteral (intramuscular) drug for three months or more, receiving it once or twice a day. The dose in the latter group of patients was the amount necessary to cause a reduction in blood pressure to within normal limits in the upright position or the maximum dose free of prohibitive side reactions if the blood pressure could not be reduced to normotensive levels. In the acute studies, there was a significant hypotensive response following administration by both the intramuscular and the intravenous routes. This was most marked in the upright position (orthostatic effect). The response was less abrupt, lasted longer, and the side reactions were less severe by the intramuscular than by the intravenous route. However, after three months, the patients who received the drug intramuscularly on a chronic basis became resistant to the drug. In only six out of sixteen patients could the hypotensive response (diastolic blood pressure reduced more than 20 mm. Hg) be maintained even though the dose was increased fivefold. Even at this dosage level, the upright blood pressure could be reduced to normotensive levels in only two patients. Therefore, it is concluded that intramuscular Regitine is a hypotensive agent that should be reserved for short term therapy such as hypertensive crises, or as interval therapy between courses of other hypotensive agents.

2. Regitine, when administered by the oral route over a prolonged period of time, caused intolerable gastrointestinal manifestations in all patients. Therefore, as an orally administered drug it is of little value in the management of hypertension. This does not indicate that the drug when administered orally is not effective in the treatment of other disease entities in which less complete adrenergic blockade is effective.

3. The effect of blood pressure reduction on cerebrovascular hemodynamics was evaluated in six patients in the supine position. Cerebral blood flow and cerebral oxygen uptake were not altered despite a significant decrease in the mean blood pressure.

REFERENCES

1. Warren, M. R.: Pharmacological Studies on 2-[N-p'-Tolyl-N-(m'Hydroxyphenyl)-Aminomethyl] Imidazoline Hydrochloride (C-7337), Federation Proc. **8**:343, 1949.
2. Trapold, J. H.: Pharmacological and Toxicological Studies on 2-[N-p'-tolyl-N- (m'hydroxyphenyl)-aminomethyl] Imidazoline (C-7337), a New Adrenergic Blocking Agent, J. Pharmacol. & Exper. Therap. **100**:119, 1950.
3. Herrold, E. A.: Pharmacologic Properties of 2-[N-p'-tolyl-N-(m'hydroxyphenyl)-aminomethyl]-Imidazoline Hydrochloride (C-7337), a Sympatholytic, Federation Proc. **8**:302, 1949.
4. Grimson, K. S.: Effectiveness of Several Adrenolytic, Sympatholytic or Ganglionic Blocking Drugs Against Acute and Chronic Neurogenic Hypertension, Am. J. Med. **7**:250, 1949.
5. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Investigation **27**:476, 1948.
6. Handley, C. A., Sigafoos, R. B., and La Forge, M.: Proportional Changes in Renal Tubular Reabsorption of Glucose and Excretion of 1-Aminohippurate With Changes in Glomerular Filtration Rate, Am. J. Physiol. **159**:175, 1949.
7. Hafkenschiel, J. H., Crumpton, C. W., Moyer, J. H., and Jeffers, W. A.: The Effects of Dihydroergocornine on the Cerebral Circulation of Patients With Essential Hypertension, J. Clin. Investigation **29**:408, 1950.
8. Moyer, J. H., Miller, S., Tashnek, A., Snyder, H., and Bowman, R.: Malignant Hypertension and Hypertensive Encephalopathy—Cerebral Hemodynamic Studies and Therapeutic Response to Continuous Infusion of Intravenous Veriloid, Am. J. Med., J. Clin. Investigation, **32**:172, 1953.
9. Kety, S. S., and Schmidt, C. F.: The Effects of Altered Arterial Tensions of Carbon Dioxide and Oxygen on Cerebral Blood Flow and Cerebral Oxygen Consumption of Normal Young Men, J. Clin. Investigation **27**:484, 1948.

Clinical Reports

MEAN SPATIAL VECTORCARDIOGRAPHY

The T Vector Changes in Hypothyroidism

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Zondek first reported the effects of myxedema on the human heart,[1] and his observations were confirmed in this country by Fahr[2] in 1925. Since that time there has been an abundant literature on the subject. The electrocardiographic changes in advanced hypothyroidism have been repeatedly described. Low amplitude of the P and T waves, T-wave inversion, and low voltage of the QRS complexes are the most common alterations. Other changes, such as delay in the auriculoventricular conduction, are less constant. Schantz and Dubbs[3] have reviewed the literature on the subject, and present a case of total auriculoventricular dissociation in which the cardiogram became normal with thyroid therapy. There are many similar papers on the electrocardiographic alterations, and all agree that most of the changes are constant and predictable. Likewise it has been repeatedly shown that the observed changes are almost always easily and promptly reversible with thyroid therapy.

The pathologic cause (or causes) for the changes is much less clear. LaDue,[4] in 1943, reviewed the literature on pathology in myxedema heart disease and presented an additional case. As had the previous authors, he reported the finding of hydropic vacuolization, loss of striation, branching, pyknotic nuclei, and irregularity in the staining properties of the muscle fibrils. The vacuoles failed to stain for fat, mucus, or glycogen. Some previous workers had considered these changes to be specific for the myxedema heart, but LaDue reported the same findings in beriberi heart, in some patients dying from noncardiac causes, and in experimental animals which had been starved. It would appear that this vacuolization, which is the principal finding (and has been constantly reported in all myxedema hearts), is not specific for this condition alone. Because of the similarity in the pathologic appearance in beriberi and myxedema hearts, LaDue treated a myxedematous patient with large doses of thiamin and vitamin B complex but without improvement. When thyroid was added to the program the

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patient promptly became better. It was his impression that a specific pathologic alteration had not been proved. Subsequent authors have agreed with his findings and conclusions.

Inasmuch as mean spatial vectorcardiography provides a method of localizing with fair accuracy the site of the pathologic processes producing abnormal cardiograms, we were interested in studying a myxedematous patient by this method. One of us, (G.E.G.) has had the opportunity of following a patient for a number of years, during which time she has been successively hyperthyroid, hypothyroid, euthyroid, again hypothyroid, and finally euthyroid. Electrocardiograms are available for each period of observation, so we were presented with an unusual opportunity to study the alterations present in each metabolic phase.

METHOD

The mean spatial vectors in this study were derived from the conventional cardiograms by the method originated by Grant.[5] The frontal plane projection of this vector is identical to the mean electrical axis described originally by Einthoven, and may be derived in the same manner. However, in practice the followers of Grant use a triaxial (for 3 extremity leads), or a hexaxial (for 6 extremity leads) figure, and derive the vector by projection methods. It is not within the scope of this paper to go into detail regarding this method, but it takes advantage of the fact that the lead which shows the greatest deflection will have its axis roughly parallel to the vector, whereas the lead which is isoelectric will have its axis at right angles to the vector. The spatial direction of the mean vector can be determined by identifying the precordial electrode position where a transitional deflection was recorded from that vector. (The transitional plane of a vector always lies at right angles to the direction of the vector.) Then by the use of models such as the one originated by Grant and Estes,[6] and modified by Urschel and Abbey,[7] it is possible to demonstrate spatially the path of the vector within the chest, to measure the direction of this path in three planes, and to record these measurements on appropriate charts.[8]

In this study we are forced to limit a portion of our study to the frontal plane projection of the QRS and T vectors, as the cardiograms did not always include unipolar chest leads (Figs. 1, 2, and 3). In Figs. 5 and 6 the chest leads were not complete, and for this reason the transitional zone for the T wave had to be approximated from the appearance of the available leads.

CASE REPORT

This 53-year-old white woman had a past history of recurrent hyperthyroidism, with thyroidectomies performed in 1927, 1930, and 1940. Within a year after her last operation, she began to develop some dyspnea and orthopnea. When first seen by one of us (G.E.G.) in October, 1946, she was complaining of these symptoms, plus some variable anterior chest distress. She had no evidence of congestive failure, but her pulse was 100, and her blood pressure 130/70 mm. Hg. Physical examination of the heart was negative, except for an apical systolic blow. The electrocardiogram on Oct. 26, 1946, was normal (Fig. 1). Her basal metabolic rate was plus 37 per cent, and she demonstrated the physical signs of hyperthyroidism. On propylthiouracil, the basal metabolic rate fell to plus 8 per cent, and a thyroidectomy was performed on Jan. 3, 1947. Pathologic report was hyperplastic goiter.

Her postoperative course was uneventful until April 16, 1947, when she was seen at 2:00 A.M. because of the abrupt onset of symptoms of shock, with marked pallor and cold perspiration. Her blood pressure was 70/60 mm. Hg and the pulse 90. Partial recovery occurred within a few hours without specific therapy. Routine count, urinalysis, and serum calcium were normal. Two basal metabolic rates obtained shortly after this attack showed readings of minus 31 and minus 33. There had been no chest pain during the attack. A cardiogram was obtained on April 21, 1947, (Fig. 2) showing marked changes as compared to the preoperative tracing. These changes were interpreted as due to postoperative hypothyroidism, and she was placed on thyroid extract, receiving 1 grain daily, with prompt clinical improvement. Her basal metabolic rate on June 17, 1947, was minus 14 per cent.

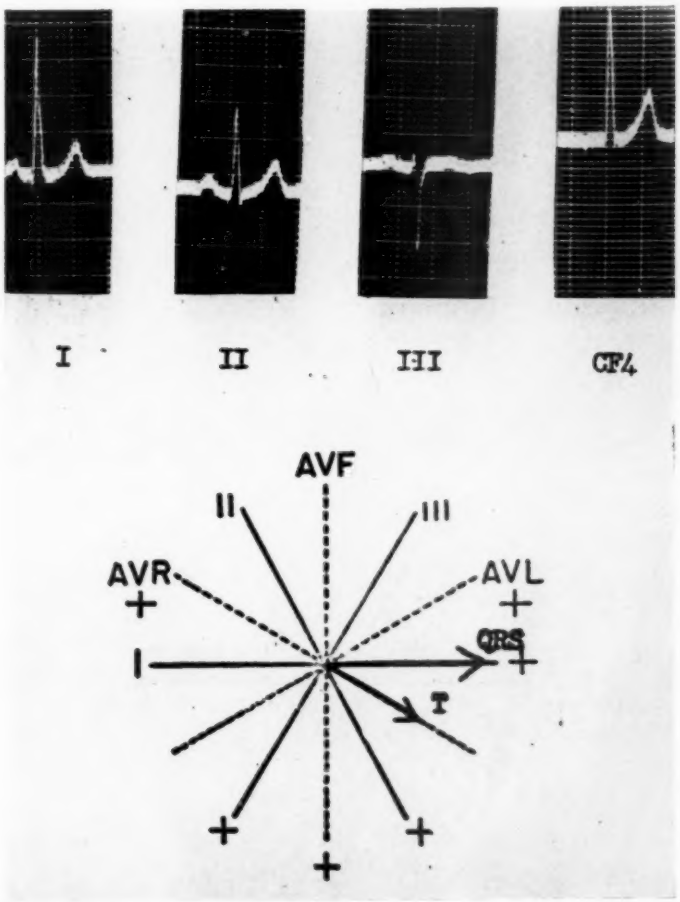

Fig. 1.—Electrocardiogram and frontal plane vectors on Oct. 26, 1946. A basal metabolic rate at this time was plus 37 per cent.

During the next four years, her course was uneventful, and a routine cardiogram which was obtained on May 26, 1950, (Fig. 3) showed a normal pattern.

In March, 1951, she began to have vague mild left-sided abdominal pain, but roentgenogram studies and symptomatic therapy were not helpful. She consulted a gastroenterologist, who diagnosed atrophic gastritis and advised her that she did not need thyroid extract therapy. Her basal metabolic rate at this time was minus 3 per cent. After discontinuing the thyroid, she soon began to note generalized numbness and weakness. She accordingly resumed the therapy

with prompt relief. In September, 1951, she developed an acute bowel obstruction, and an exploratory laparotomy was performed on Sept. 12, 1951. She was found to have a benign jejunal polyp, and 12 inches of the jejunum were resected. Her thyroid extract was discontinued prior to operation, but within less than two weeks she again began to develop severe weakness and a variable and slow cardiac rhythm. She was placed on quinidine, on Sept. 24, 1951, receiving 0.2 Gm. every six hours.

On Sept. 25, 1951, she was again seen by one of us (G.E.G.) and a cardiogram was obtained, (Fig. 4) which showed changes of the same type as those noted in her previous episode of hypothyroidism in 1947. Quinidine was discontinued, and she was immediately placed on thyroid extract therapy. Clinical improvement was prompt and has persisted to the present time. A routine cardiogram was obtained on Feb. 4, 1952 (Fig. 5), once again showing a normal pattern.

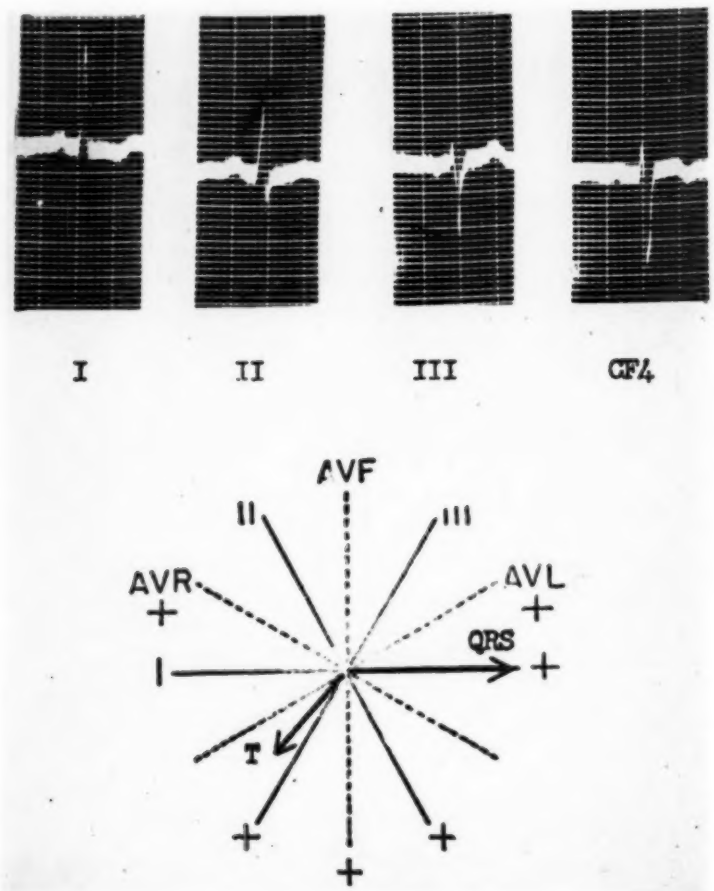

Fig. 2.—Electrocardiogram and frontal plane vectors on April 21, 1947. Basal metabolic rate at this time was minus 33 per cent.

DISCUSSION

Grant and associates[9] have demonstrated the importance of the QRS-T angle in evaluation of abnormalities of the T wave. In the majority of normal subjects this angle does not exceed 50°. In other words, the vector path of depolarization and the vector path of repolarization form an angle between them of less than

50°. It is then apparent that any process which alters the path of repolarization will alter this angle. It is of particular interest in this study of thyroid alterations that the QRS, or depolarization process, is relatively stable, and shows little alteration in disorders which cause marked change in the T, or repolarization, process. This is true not only in this instance, but in most other disorders which affect the T process, so that the QRS vector remains relatively stable and provides a ready standard of reference for evaluating T alterations. This is graphically evident in this study, as Figs. 1 through 5 will show that the QRS remained relatively stable throughout this entire period of study.

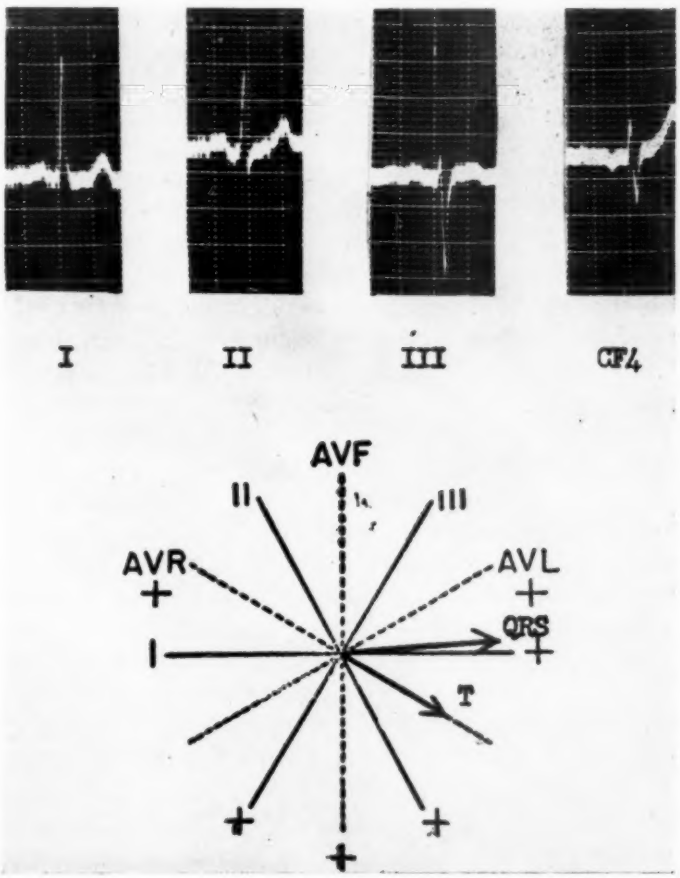

Fig. 3.—Electrocardiogram and frontal plane vectors on May 26, 1950. Basal metabolic rate was not obtained at the same time, but the patient was on thyroid extract therapy, and basal metabolic rates during this period were ranging between minus 3 per cent and minus 14 per cent.

Grant has classified T-wave, or more properly, T vector, abnormalities into two basic groups. In *Secondary T* vector alterations, the abnormal T direction results from an abnormality in the QRS vector, as in bundle branch block. Because of the conduction disturbance, the stimulus for depolarization is distributed to the various parts of the heart by abnormal routes. Since T forces can be

generated only after the release of QRS forces, a change in sequence of the latter must result in abnormalities of the former. The T process at each cell is normal, unlike the situation in the other type of T vector abnormality. In *Primary T* vector alterations there is an actual change in the intrinsic biophysical cellular process which constitutes repolarization. This change in effect prolongs the T process at the affected region, so that these T vectors do not act in the formation of the mean spatial T vector. Thus the T vectors from the unaffected regions of the heart dominate the mean spatial T vector, which therefore tends to point away from the site of the abnormality. This is the type of T vector alteration with which we are concerned in hypothyroidism, although the basic cause for the delay in repolarization is not clearly defined. As has been previously shown,[4] there are microscopic changes in the myocardium (vacuolization, etc.,) and it can be deduced hypothetically that these physical alterations result in delay in the cellular biophysical process which constitutes repolarization. Grant has listed three principal causes of T vector abnormality—ischemia, myocardial pressure variations (as in ventricular hypertension), and digitalis effects. The effect of ischemia, as in coronary artery disease, is relatively self-explanatory, though the different effect of subendocardial and subepicardial ischemia is not too satisfactorily explained, in our opinion. Ventricular hypertension alters repolarization by slowing the process in the muscle immediately adjacent to the ventricular chamber. Digitalis (and some other drugs to a lesser degree) so shortens the length of time between the QRS and T processes that it causes the mean QRS and T vectors to be nearly 180° from each other. It is difficult to relate the changes in hypothyroidism to any of these basic causes, although it would appear most similar to the ischemia effect.

In discussing this problem, it will be best to consider each separate cardiogram and the appropriate vector analysis. In Fig. 1, we have shown the vectors during the period when the patient was definitely hyperthyroid. As is well known, hyperthyroidism exerts inconstant and variable effects on the cardiogram, and in this instance the tracing would be considered normal. As may be seen in the frontal plane presentation of the QRS and T vectors, the QRS-T angle is 30°, well within normal limits. The heart is in a relatively horizontal position electrically and, as has been previously noted, it remained so during the entire period of observation. The QRS vector, therefore, extends almost directly leftward in the frontal plane.

In Fig. 2, an entirely different picture is presented. The patient is now in a state of considerable hypothyroidism, having had her thyroidectomy over three months previously, and receiving no thyroid extract therapy. The QRS has not been altered, but the T process has been markedly changed. The T vector has swung to the right and inferiorly, widening the QRS-T angle to 130°, resulting in an inversion of T in Lead I, a decrease of T in Lead II, and an increase in Lead III. It is also to be noted that there is inversion of T in CF_4, but this cannot be used in the vector analysis. That there is marked change in the T-waves across the precordium is shown in subsequent illustrations. It has been previously stated that the abnormal T tends to point away from the involved area, because the noninvolved regions generate normal T vectors which dominate the mean

spatial T. In this instance we would have to conclude that the abnormality was largely in the left ventricle, as the T vector points away from it. It may be that the greater mass of the left ventricle is more affected by the changes of hypothyroidism than is the relatively thin-walled right ventricle.

In Fig. 3 we see the vectors after the patient has been restored to a euthyroid state by the administration of thyroid extract. The T vector has once more

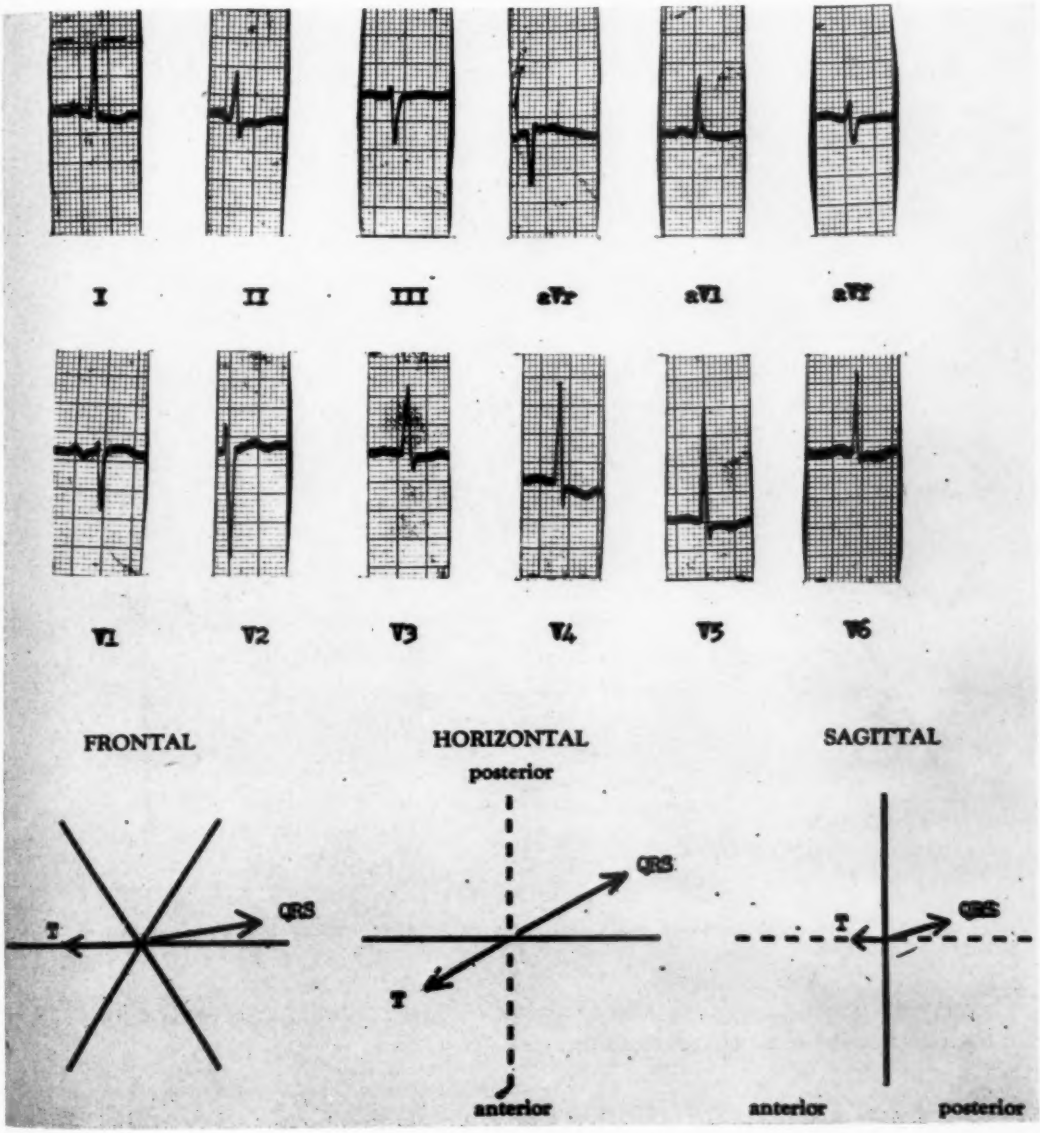

Fig. 4.—Electrocardiogram and vector analysis on Sept. 25, 1951. The patient had undergone a bowel resection on Sept. 12, 1951, and had been given no thyroid extract following the surgery.

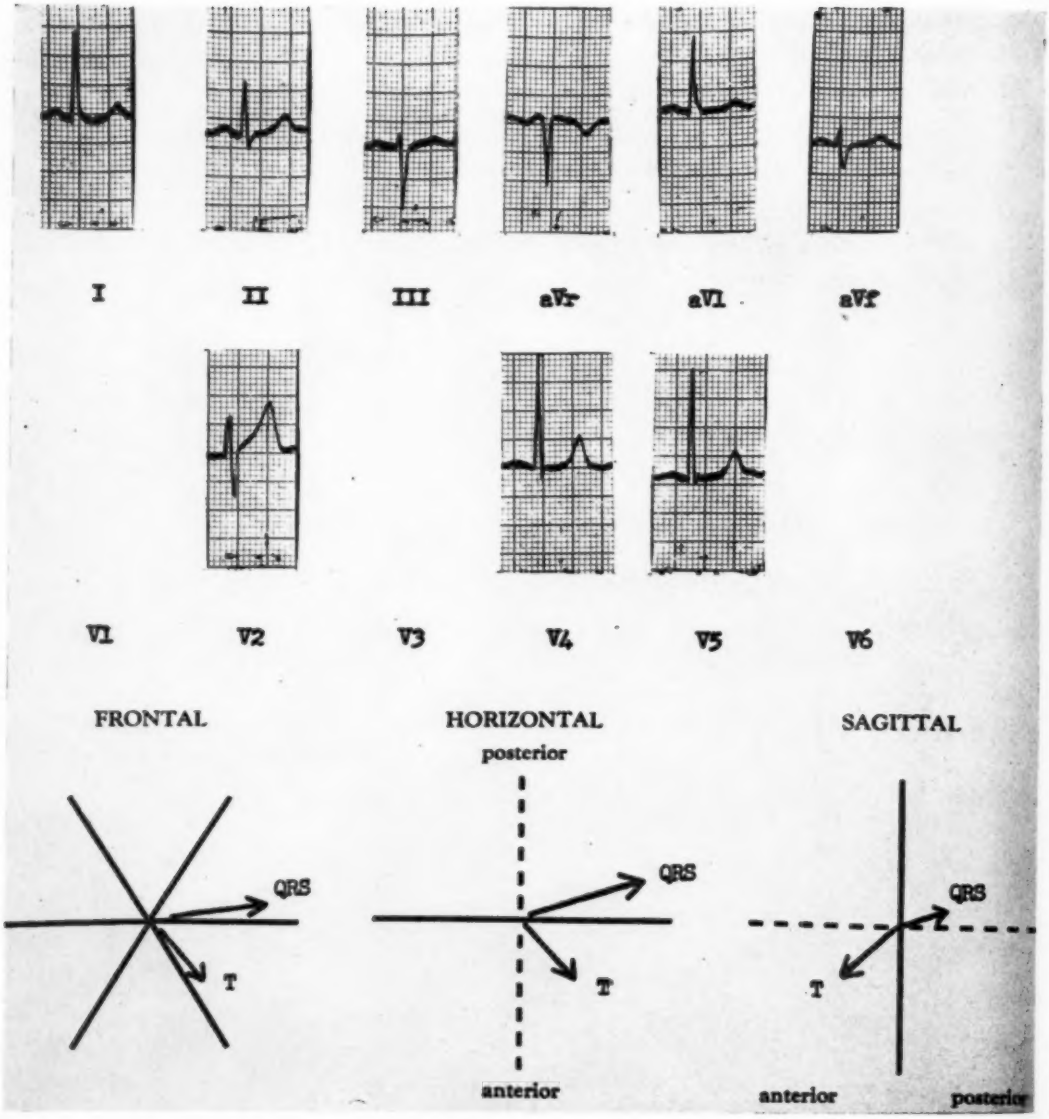

Fig. 5.—Electrocardiogram and vector analysis on Feb. 4, 1952. The patient was once more receiving thyroid extract.

assumed a normal position, and the conventional cardiogram is quite similar to the one noted before thyroidectomy.

In Fig. 4, we see once more the changes brought on by hypothyroidism. The patient had not been taking thyroid extract for thirteen days prior to this cardiogram. That symptoms and signs of hyperthyroidism developed so quickly was probably due to the stress of the postoperative state following the bowel resection.

For the first time we have a 12-lead cardiogram available, and can demonstrate not only the markedly widened QRS-T angle in the frontal plane (over 180°), but we also see that there is T-inversion over the left side of the precordium.

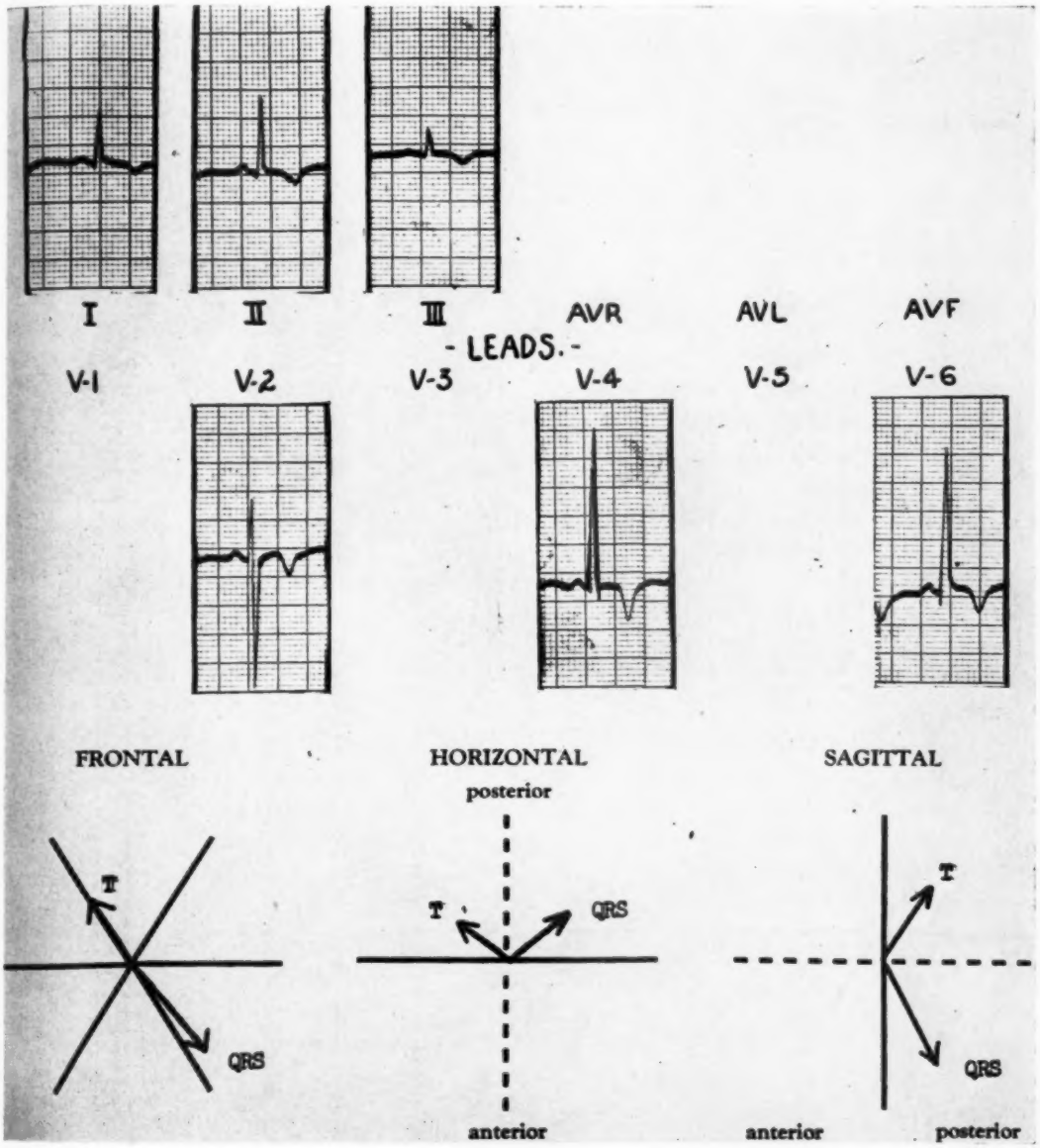

Fig. 6.—The electrocardiogram and vector analysis from a patient with acute pericarditis. This tracing was obtained six weeks after the onset of illness.

When this is measured on the vector model previously mentioned, and drawn on the appropriate graphs it can be seen that the T vector is pointing to the right, slightly anterior horizontally, and anteriorly in the sagittal plane. If one imposes

these graphs over the outlines of the heart in these three planes, it is very easily shown that the T vector in this instance is pointing almost directly away from the left ventricle.

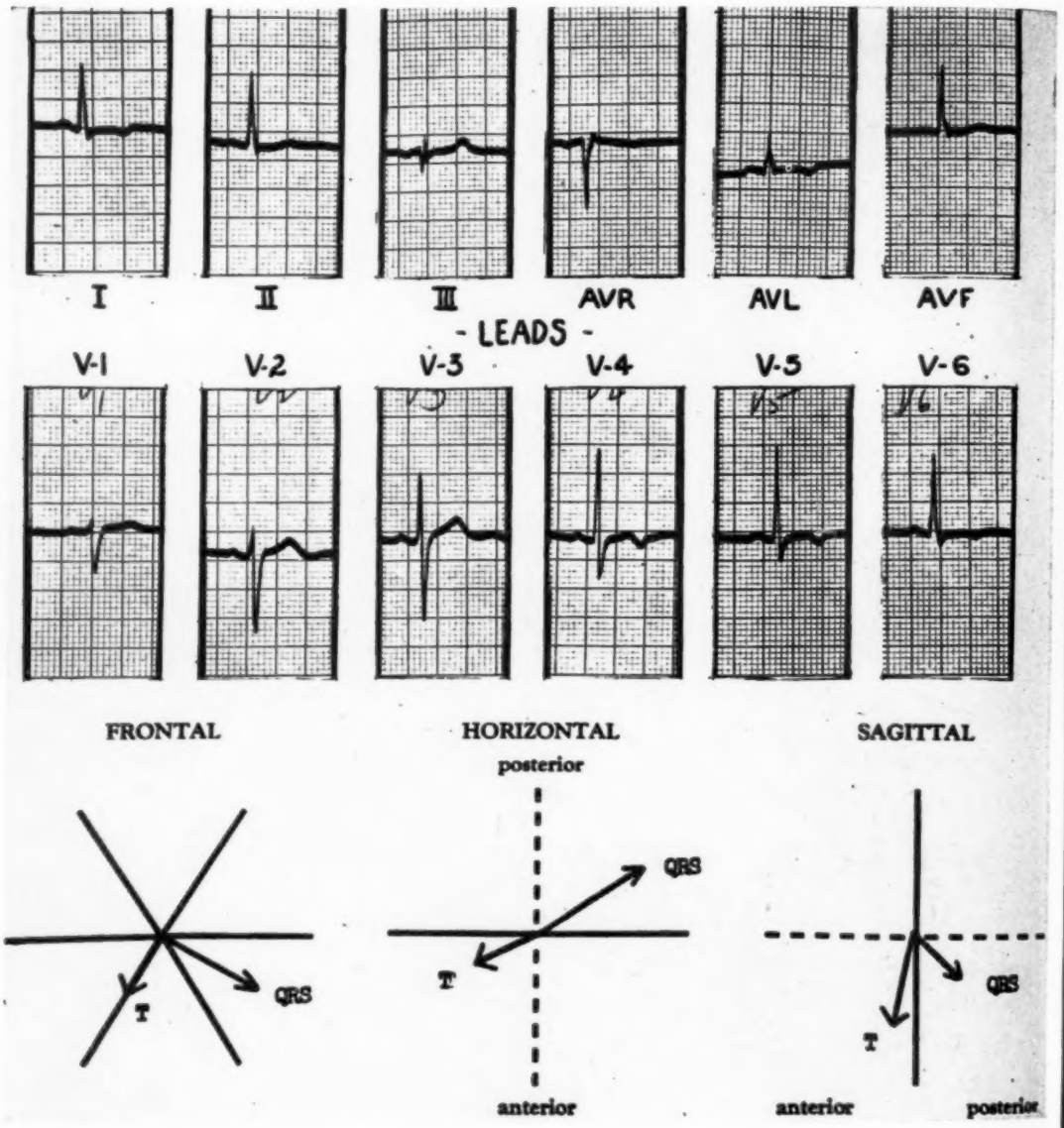

Fig. 7.—The electrocardiogram and vector analysis from a patient who had been hypertensive for at least ten years.

In Fig. 5, the patient is once more in a euthyroid state, and her cardiogram has returned to normal. The QRS-T angle is once again normal.

To compare these T vector alterations to those resulting from other causes we have included two additional cardiograms, with appropriate vector analysis.

In Fig. 6 is shown the cardiogram of a 32-year-old white man who had been suffering from acute pericarditis for six weeks. The T-wave changes are the classical ones which are to be expected at this stage of the disease in many patients. Urschel and associates[10] have shown that the T-wave alterations in pericarditis appear in full degree only after several weeks of illness, apparently resulting from subepicardial alterations which develop slowly and are not directly the result of the increased intrapericardial pressure, as the T-wave inversion usually reaches its greatest magnitude after the heart has returned to normal or nearly normal size. Of principal interest in this vector analysis, is the fact that the T vector is pointing toward the right shoulder, or away from all of the muscle mass of the heart. Since pericarditis is usually a diffuse process involving all portions of the pericardium (and epicardium) we should then be able to predict that a vector which points away from the involved area could only point to the region of the right shoulder. This is borne out by this demonstration. To contrast this we have shown in Fig. 7 the cardiogram and vector analysis of a 41-year-old white woman who has been hypertensive for at least ten years. When this is compared with the cardiograms and vectors shown in Figs. 2 and 5, considerable similarity is noted. It is well recognized that the vector changes in hypertension result from alterations in the left ventricle, and that the T vectors thus created point away from that ventricle. This is well illustrated in this patient, who was chosen for this presentation because her vector changes are characteristic but moderate. In more severe hypertensive cases we get more alteration in the QRS-T angle, with inversion of T 2 as the angle widens.

SUMMARY AND CONCLUSIONS

1. We have presented a patient who was of particular interest in that she showed five distinct phases of thyroid activity, with cardiograms available at all stages—hyperthyroid, hypothyroid, euthyroid, hypothyroid, and again euthyroid. It was therefore possible to follow the course of the T-wave, or T vector, alterations through these periods of altered metabolism. We have shown these cardiograms with appropriate vector analysis by the method originated by Grant. For comparison we have included a cardiogram with vector analysis from a patient with pericarditis, and another from a patient with long-standing arterial hypertension.

2. The alterations in the T vector in hypothyroidism appear to be due to altered cellular metabolism which retards the process of repolarization in the involved muscle.

3. From the direction of the altered T vector in this patient it also appears that the principal involvement is in the myocardium of the left ventricle. We have no ready explanation for this, unless it is in connection with the greater mass of muscle and the greater work-load of the left ventricle. The vector analysis closely resembles that seen in chronic arterial hypertension.

The authors are indebted to Mr. Denton C. Abbey for technical assistance.

REFERENCES

1. Zondek, H.: Das Myxodem Herz, München med. Wchnschr. **65**:1180, 1918.
2. Fahr, G.: Myxedema Heart, J. A. M. A. **84**:345, 1925.
3. Schantz, E. T., and Dubbs, A. W.: Complete Auriculoventricular Block in Myxedema, With Reversion to Normal Sinus Rhythm on Thyroid Therapy, AM. HEART J. **41**:613, 1951.
4. LaDue, J. S.: Myxedema Heart; Pathological and Therapeutic Study, Ann. Int. Med. **18**:332, 1943.
5. Grant, R. P.: Spatial Vector Electrocardiography. A Method for Calculating the Spatial Electrical Vectors of the Heart From Conventional Leads, Circulation **2**:576, 1950.
6. Grant, R. P., and Estes, E. H.: Spatial Vector Electrocardiography, Philadelphia, 1951, The Blakiston Company.
7. Urschel, D. L., and Abbey, D. C.: Modification of a Vector Model to Provide Accurate Recording of Mean Vector Positions in Three Planes of Space, AM. HEART J. **44**:372, 1952.
8. Urschel, D. L., and Abbey, D. C.: Mean Spatial Vectorcardiography. The Normal QRS and T Vectors, AM. HEART J. **45**:55, 1953.
9. Grant, R. P., Estes, E. H., and Doyle, J. T.: Spatial Vector Electrocardiography. The Clinical Characteristics of ST and T Vectors, Circulation **3**:182, 1951.
10. Urschel, D. L., Bondy, P. K., and Salley, S. M.: Acute Pericarditis. A Graphic Correlation of the X-ray, Clinical and Electrocardiographic Findings, New England J. Med. **233**:399, 1945.

PERSISTENT COMMON ATRIOVENTRICULAR CANAL

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WITH SURGICAL correction and amelioration of a greater number of congenital cardiac anomalies, clinical recognition of all varieties of these anomalies becomes an increasingly important duty. While it is important to recognize cases in which surgical treatment is likely to be successful, it is equally important that those cases which are not amenable to surgical treatment should be diagnosed correctly by clinical means in order to prevent unnecessary operations. Recognition of the more unusual congenital cardiac anomalies depends upon familiarity with the clinical characteristics of these defects. It is the purpose of this report to record the clinical findings in a child with one of the more unusual congenital cardiac anomalies: persistent common atrioventricular canal.

CASE REPORT

The patient was a white boy infant 3 months of age, at the time of his first examination on April 18, 1951. No maternal infections had been encountered during the pregnancy. The child was born at full term. No cyanosis had been observed at birth or in the period of early infancy. Failure to gain in weight was observed, and at 3 months the infant weighed only 9 pounds and 4 ounces. A slight cough had been present, and grunting respiration had been recently noticed. Occasionally, regurgitation of food had occurred.

On physical examination the color of the mucous membranes was good and appreciable cyanosis was absent. No evidence of mongolism was observed. The precordium was prominent. Aortic and mitral systolic murmurs were heard. These murmurs were both Grade 2. No diastolic murmurs were present. Results of examination of the abdomen were negative. No clubbing of the digits was observed. The femoral arterial pulsations were present.

The results of blood examination were as follows: the concentration of hemoglobin was 12.5 Gm. per 100 c.c. of whole blood (86 per cent). Erythrocytes numbered 4,500,000 per c.mm. of blood. The leukocyte count and differential count were normal. The electrocardiogram revealed left axis deviation with large QRS complexes in Leads I and III and in the AV_L lead (Fig. 1). The P-R interval was 0.16 second and the QRS complex measured 0.08 second in duration. The T waves were poorly defined, being isoelectric in Lead I and AV_L and of low amplitude in Lead III and AV_F. The roentgenographic examination of the thorax revealed marked enlargement of the cardiac silhouette (Fig. 2). This was predominantly enlargement in the anticipated position of the left ventricle, but prominence of the area created by the pulmonary conus was also observed The lung fields were clear. There was a left aortic arch.

The left axis deviation observed in the electrocardiogram, in association with the absence of cyanosis, suggested the possibility of an associated valvular atresia, most likely an aortic atresia. At the same time the absence of appreciable cyanosis and the presence of biphasic complexes of large amplitude suggested a functional cor triloculare. The patient's congenital cardiac lesion was not considered amenable to surgical treatment.

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The infant was seen again three months later. Development had been somewhat improved. No cyanosis was present. The aortic and apical systolic murmurs were unchanged.

In March, 1952, at the age of 14 months the infant was admitted to Mound Park Hospital because of fever, cough, and shortness of breath. Cyanosis was more marked. The physical examination, with the exception of crackling râles at both pulmonary bases, was unchanged. A temperature of 102° F., which was present upon admission, responded to penicillin and the child was dismissed after five days. One month later the infant was readmitted to the hospital with considerable increase in dyspnea, cyanosis, and evidence of congestive heart failure. The hepatic margin was palpable 3 cm. below the right costal margin. Roentgenographic examination

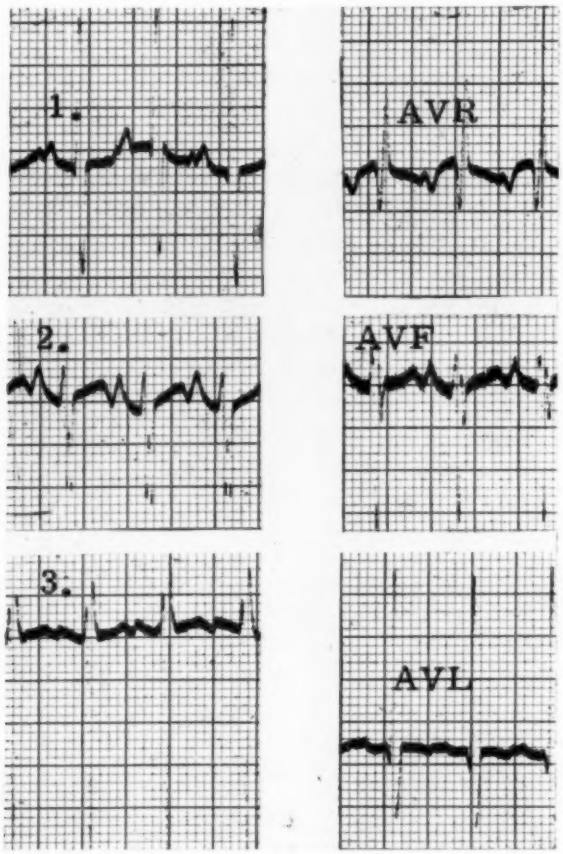


Fig. 1.—Electrocardiogram taken April 18, 1951, revealing large biphasic complexes with left axis deviation.

revealed in addition to cardiac enlargement marked passive congestion of the lungs. With oxygen and digitalization some improvement was observed. He was dismissed after eleven hospital days. On May 16, 1952, the child was readmitted with congestive cardiac failure. Death occurred on the afternoon of his admission at the age of 16 months.

At *necropsy*, the pertinent findings were confined to the heart and lungs. The atrial septum had a large defect involving its lowest portion. The upper end of this defect was crescent shaped; the lower end of the defect was formed by atrioventricular valvular tissue and the closely associated ventricular septum (Fig. 3, *A*). The defect, which extended the full anteroposterior diameter of the atrial septum, measured 3.6 cm. from before backward and 1.8 cm. from above downward.

Just above the defect was atrial septal tissue in which could be identified the upper limbus of the fossa ovalis. There was a probe patent foramen ovale (Fig 3, *B*).

The atrioventricular valves were abnormal. When viewed in the conventional manner, the tricuspid valve showed its septal leaflet to have a cleft dividing the leaflet into anterior and posterior halves (Fig. 4, *A*). From the lower aspect of both of these, tissue inserted into the underlying ventricular septum, thereby making these valvular elements relatively fixed. Viewed from the left side, the anterior leaflet of the mitral valve was cleft (Fig. 3, *A*). The posterior one-half of the cleft anterior leaflet was, like the septal leaflet of the tricuspid, intimately attached to the underlying ventricular septum by short chordae. The anterior one-half of the anterior leaflet was relatively free, although at its medial aspect it, too, was attached to the underlying muscular portion of the ventricular septum by short chordae. When the atrioventricular valves were viewed as a unit, it was apparent that a common atrioventricular valve existed. The anterior leaflet of the common valve was formed by what might be designated as the anterior halves of the cleft anterior mitral and the septal tricuspid leaflets. The posterior leaflet of the common atrio-

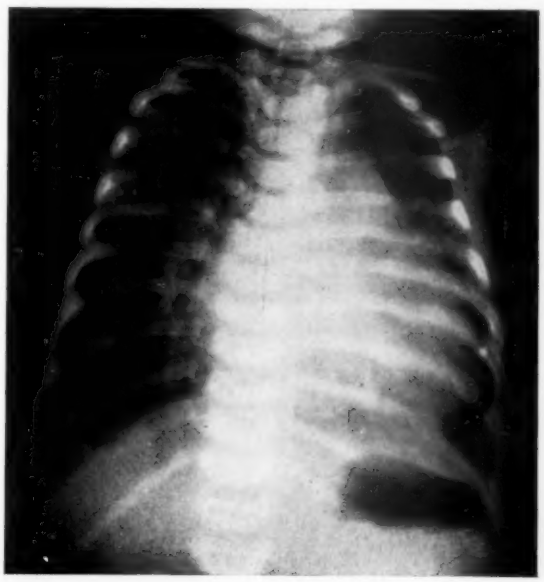


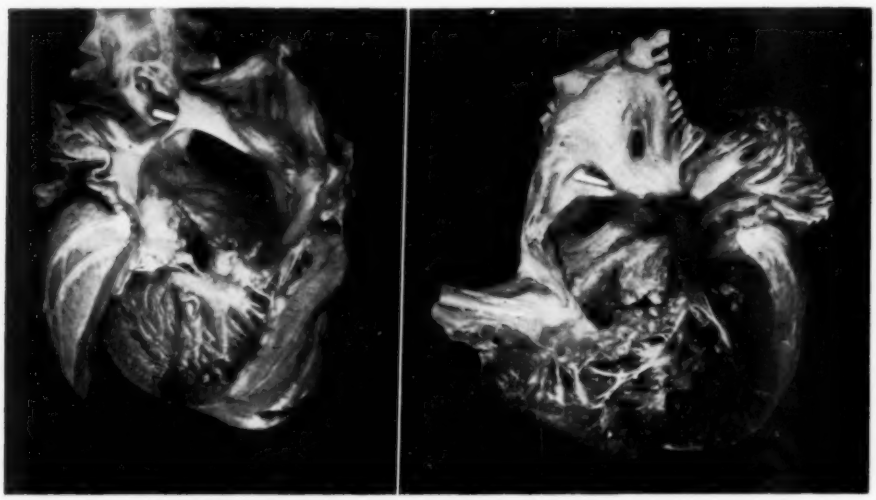
Fig. 2.—Roentgenogram of the thorax. Marked cardiac enlargement.

ventricular valve was formed by the posterior one-half of the cleft anterior mitral leaflet and the posterior one-half of the cleft septal tricuspid leaflet. It was apparent that the elements of the posterior leaflet of the common atrioventricular valve were intimately fused with the underlying ventricular septum and probably played little role in closing the atrioventricular valve.

The two ventricles were of approximately equal thickness; the left ventricle measured 0.9 cm. and the right ventricle measured 1.1 cm. in thickness. The cavity of the right ventricle was larger than the cavity of the left ventricle (Fig. 4, *B*). The great vessels were properly related to each other. The pulmonary trunk was fully as thick walled as the aorta and had the same yellow color as the aorta. The membranous portion of the ventricular septum was intact. The pulmonary trunk measured 2.6 cm. in diameter, and the ascending aorta measured 2.3 cm. in diameter. The ductus arteriosus was closed. The aortic arch was in a normal position. The pulmonary veins entered the left atrium in a normal manner. The systemic veins entered the right atrium in a normal manner. The lungs were uniformly firm and purple as though containing considerable hemorrhage.

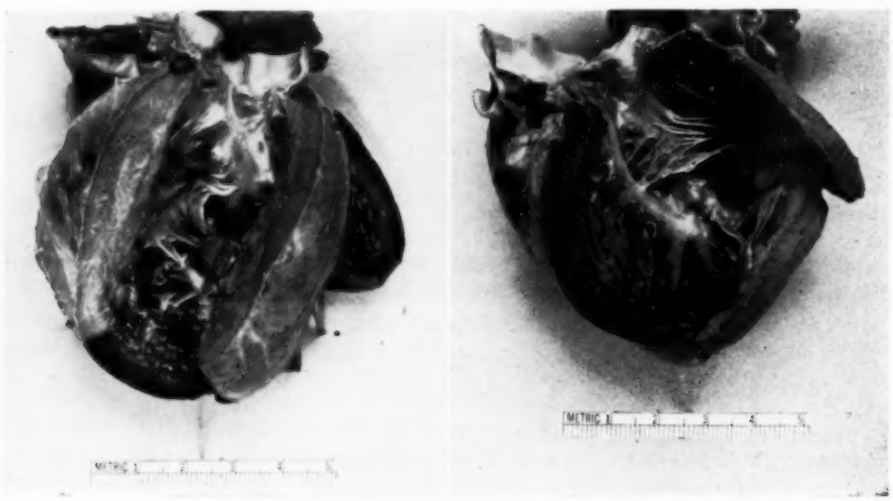
The following gross anatomic diagnoses were made: common atrioventricular canal and valve; defect of lower part of atrial septum; hypertrophy of the right ventricle; pulmonary congestion and hemorrhage.

Histologically the lungs revealed tremendous congestion and edema. There was only an occasional focus of alveolar hemorrhage (Fig. 5, *A*). The pulmonary vessels revealed moderate degrees of medial hypertrophy in the muscular arteries (Fig. 5, *B*). These vessels also were characterized by prominent internal and external elastic membranes. The larger muscular



A. *B.*

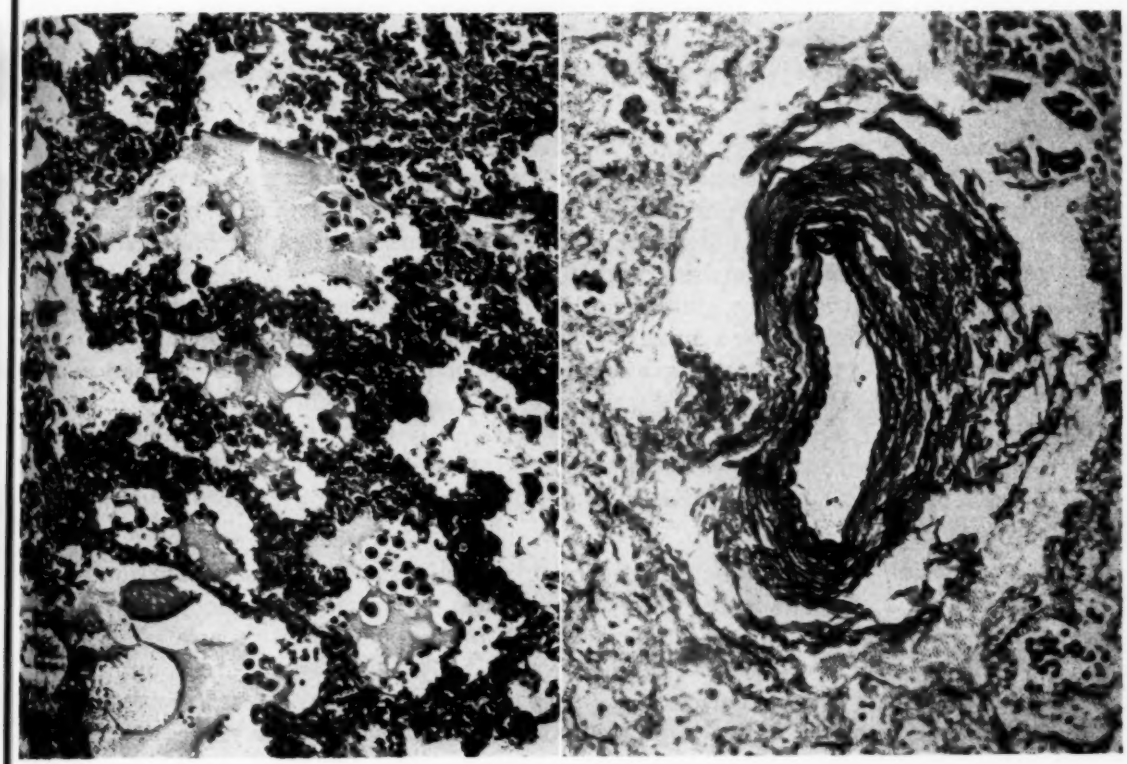
Fig. 3.—*A*, Left side of the heart. Defect in lower part of atrial septum. Cleft mitral valve. Also probe patent foramen ovale. *B*, Right side of the heart. Probe in the patent foramen ovale. Cleft tricuspid valve. Defect in lower part of atrial septum. Hypertrophy of right ventricle.



A. *B.*

Fig. 4.—*A*, Right ventricle. Right ventricular hypertrophy. *B*, Left ventricle. Cleft mitral valve.

arteries revealed the presence of elastic fibers within the thickened media. In the alveolar spaces there were small numbers of pigment-laden macrophages. The final histologic diagnosis was severe pulmonary congestion and edema with focal hemorrhage.*



A. *B.*

Fig. 5.—Photomicrographs of lung. *A*, Marked congestion and edema (Hematoxylin and eosin ×140). *B*, Muscular arteries. Medial hypertrophy. Prominence of elastic tissue (Verhoeff's elastic tissue stain and counterstained with van Gieson's connective tissue stain ×100).

COMMENT

Persistent common atrioventricular canal is an unusual congenital cardiac anomaly. In a previous report, Rogers and Edwards[1] reviewed fifty cases from the literature and reported five additional cases of their own. Other cases had been mentioned previously by Bredt,[2] Philpott,[3] and Gibson and Clifton,[4] but as these cases were not illustrated or described they were not included in the review of Rogers and Edwards. The probable embryologic relationship of persistent common atrioventricular canal and congenital aneurysm of the membranous ventricular septum has also been discussed recently.[5]

Important clinical manifestations in this case were consistent with those recorded in the series reviewed by Rogers and Edwards.[1] The survival age of 16 months is consistent with the previous series; death occurred at an early age with

*We are indebted to Dr. J. E. Edwards for assistance in pathologic anatomy in this case.

more than one-half of the patients dying in the first year of life. The median age of death was 10 months. Systolic murmurs heard in this case are the rule and the anticipated finding in this anomaly. Cyanosis may be absent or minimal in degree in this anomaly. Cardiac enlargement was demonstrated both roentgenographically and by necropsy. While both ventricles were large, the major portion of the enlargement was the result of right ventricular hypertrophy. Mongolism, which was recorded in seventeen of the fifty-five cases of Rogers and Edwards, was absent in this case.

The electrocardiographic findings in this case are of importance since previous cases were not studied electrocardiographically. Large biphasic ventricular complexes were observed, consistent with the electrocardiographic findings observed in a common ventricle. Left axis deviation, which was present, is not commonly observed in congenital cardiac disease. In cyanotic congenital heart disease, left axis deviation is most commonly associated with tricuspid atresia. Precordial leads would probably have been helpful in more accurate determination of the ventricular enlargement which, in this case, was more right-sided than left-sided. This, therefore, revealed the inadequacy of the limb leads alone, influenced as they doubtless were by the cardiac position. Also, the diphasic QRS waves of great amplitude in Lead I are not characteristic of left axis deviation per se.

Physiologically the congenital cardiac anomaly under discussion functioned as an atrial septal defect. The short chordae tendineae attaching the atrioventricular valve to the ventricular septum undoubtedly were associated with mitral insufficiency and tricuspid insufficiency. The resultant mitral regurgitation would of course accentuate the effects of the atrial septal defect, resulting in a greater degree of left-to-right shunt of blood within the heart. The atrial septal defect and the mitral insufficiency were the probable factors leading to the excessive pulmonary blood flow, which contributed to the death of this patient.

The clinical impression at the time of examination at 3 months of age was that of functional cor triloculare. This was considered in view of what appeared to be adequate pulmonary blood flow with relative decrease in aortic or systemic blood flow. Physiologically the anomaly of persistent common atrioventricular canal is best regarded as an atrial septal defect rather than a two or three chambered heart. These findings were confirmed at necropsy, the pulmonary trunk being larger than the ascending aorta, and the lungs apparently receiving a greater volume of blood than the systemic circulation. Excessive pulmonary blood flow, which was manifested histologically by an extreme degree of pulmonary edema and congestion, seems to have been the major factor in the death of this infant.

Aortic atresia was considered in the clinical diagnosis in view of the left axis deviation observed in the electrocardiogram together with the absence of external cyanosis. Relative decrease in aortic flow in comparison to the pulmonary flow was probably present in view of the relative size of the pulmonary trunk and the aorta. The pulmonary artery resembled the aorta in thickness and in diameter.

The absence of appreciable cyanosis, in spite of common admixture of blood in the common atrial cavity and common ventricular cavity, is probably explained by the adequate pulmonary blood flow through a large pulmonary trunk with adequate oxygenation of blood in the lungs.

SUMMARY

An additional case of persistent common atrioventricular canal is reported. Electrocardiographic findings of biphasic ventricular complexes were observed. Necropsy findings were typical of this congenital cardiac anomaly. A clinical diagnosis of functional three chambered heart had been made. Excessive pulmonary blood flow as evidenced by severe pulmonary congestion, edema, and focal hemorrhage appears to have existed and the resulting complications appear to have constituted the cause of death.

REFERENCES

1. Rogers, H. M., and Edwards, J. E.: Incomplete Division of the Atrioventricular Canal With Patent Interatrial Foramen Primum (Persistent Common Atrioventricular Ostium). Report of Five Cases and Review of the Literature, AM. HEART J. **36**:28, 1948.
2. Bredt, H.: Die Missbildungen des Menschlichen Herzens, Ergebn. d. allg. Path. u. path. Anat. **30**:77, 1936.
3. Philpott, N. W.: Relative Incidence of Congenital Cardiac Anomalies in Montreal Hospitals, J. Tech. Methods **15**:96, 1936.
4. Gibson, Stanley, and Clifton, M. M.: Congenital Heart Disease: A Clinical and Postmortem Study of One Hundred and Five Cases, Am. J. Dis. Child. **55**:761, 1938.
5. Rogers, H. M., Evans, I. C., and Domeier, L. H.: Congenital Aneurysm of the Membranous Portion of the Ventricular Septum; Report of Two Cases, AM. HEART J. **43**:781, 1952.

CONGENITAL ELASTIC BAND OF AORTIC VALVE

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THE interest in congenital cardiac diseases has been increasing in recent years. The research work of Taussig, Blalock and others has given greater knowledge of these lesions. The interest is now furthered, since the surgeons are dealing with and operating on more cases of congenital heart disease.

From 1947 until 1951, among 500 autopsies, we found two cases of very interesting congenital aortic valve anomalies. A review of the literature up to 1951 failed to disclose any similar case. Our first case was in a stillborn infant and the second in a 32-year-old man.

CASE REPORTS

Case 1.—Reg. 78267, was a stillborn white boy whose mother, a primipara, had a laborious delivery in which forceps had to be used. Serologic reactions for syphilis were negative.

The autopsy disclosed petechial hemorrhages on the pleural surfaces. Both lungs showed no aeration. The parietal bones overlapped the frontal bone. There was a recent erosion on the left frontal region. The heart was externally normal. On the aortic valve we found an elastic band crossing the large axis of the aortic ring in the region of the upper part of the cusps, measuring 1.3 cm. in extension and 0.2 cm. in thickness. One of the extremities of this band was firmly attached to the aortic wall, between the posterior and left cusps and the other extremity between the right and posterior cusps (Figs. 1, 2, and 3). No other anomaly was found in the heart or in any other organ.

On microscopic examination a large amount of amniotic squamous cells were found in the bronchi and pulmonary alveoli. The congenital aortic band was composed, in general, of elastic tissue such as is found in the aortic wall. The elastic tissue was arranged in irregular bundles and thin ribbons interspersed with dense fibrous tissue. The surface was covered with endothelium. The elastic tissue was very well brought out by Weigert and Sheridan stains. At certain points the endothelium was found to be thickened. The Mallory-Heidenhaim stain showed the presence of young connective tissue. The elastic tissue of the anomalous band emerged into the normal elastic tissue of the aortic wall.

Autopsy diagnosis: Congenital elastic band of the aortic valve.

Case 2.—Reg. 30220. A 32-year-old white man had a history of frequent epistaxis. In July, 1949 he became dyspneic, coughed up yellowish sputum, was feverish, lost his appetite, and developed insomnia.

On physical examination the aorta was palpable over the suprasternal region. The vessels of the neck were turgid even in lateral decubitus. There was a systolic-diastolic thrill at the apex of the heart, more conspicuous when the patient was in the left lateral decubitus. A systolic and diastolic murmur was heard in the aortic area, the systolic was propagated to the vessels of the neck and the diastolic was musical and propagated to the left side of the sternum and the apex. Strong systolic and diastolic murmurs were heard at the apex.

The liver was palpable two fingers below the costal margin. Râles were heard at the pulmonary bases. Roentgenogram of the heart revealed hypertrophy of the left side of the heart cavities. In November edema of both legs was apparent, and there were progressing symptoms of

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cardiac failure. The diagnosis was aortic insufficiency and stenosis, and congestive heart failure. Digitalis, mercurialis, and sedatives were prescribed.

In January, 1950, the patient developed symptoms of more intense cardiac failure and irregular cardiac rhythm. The liver margin was, then, 6 cm. below the costal margin. Roentgenogram

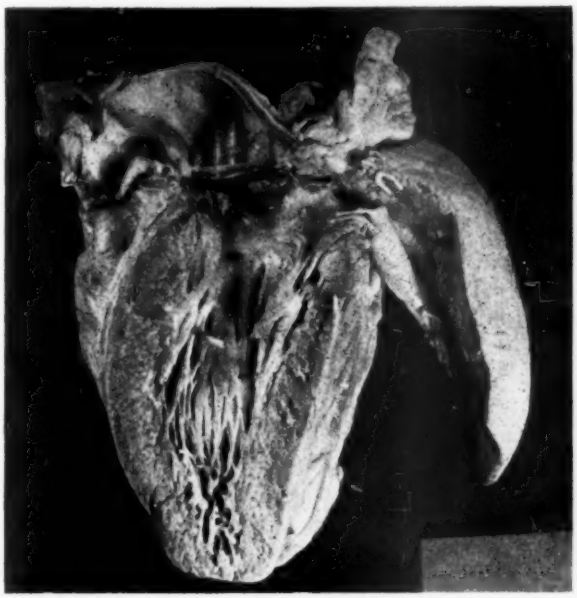

Fig. 1.—(Case 1.) Picture of the heart showing the left ventricle and the aorta. Notice the elastic band crossing the lumen of the vessel.

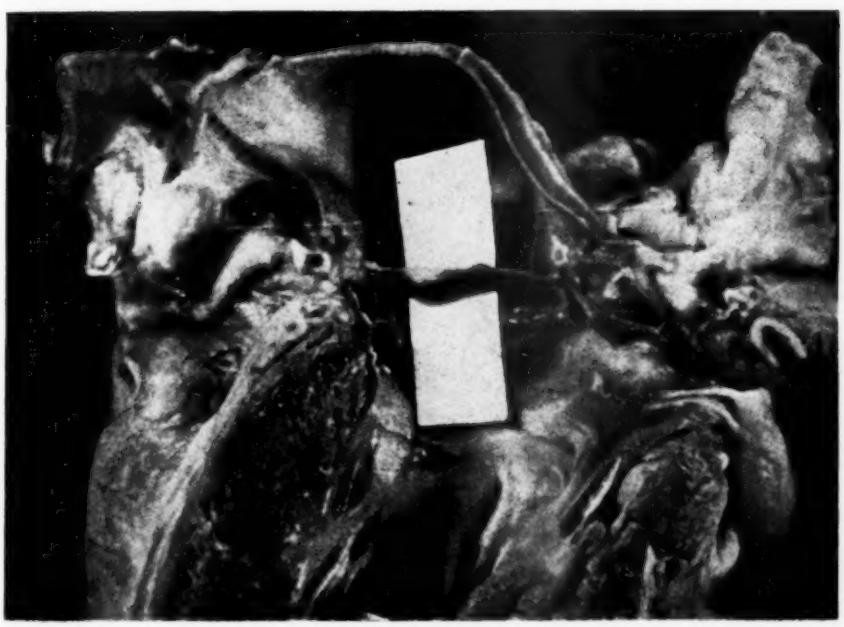

Fig. 2.—(Case 1.) The elastic aortic band is shown in detail.

revealed enlargement of all the heart cavities, condensation of pulmonary bases, and fluid in the right pleural space. The treatment prescribed was: cardiotonics, mercurialis, vitamins, glycosides, streptomycin, aminophylline, sedatives, and other drugs.

Laboratory findings: Jan. 20, 1950, the leukocyte count was 15,000, 89 per cent of the leukocytes were polymorphonuclear cells; the sedimentation rate was 40 mm. in the first hour and 70 mm. in the second (Westergren). March 9, 1950, the sedimentation rate was 70 mm. in the

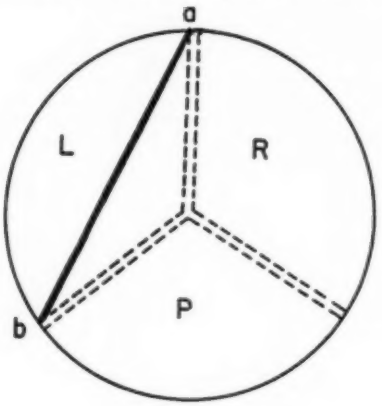

Fig. 3

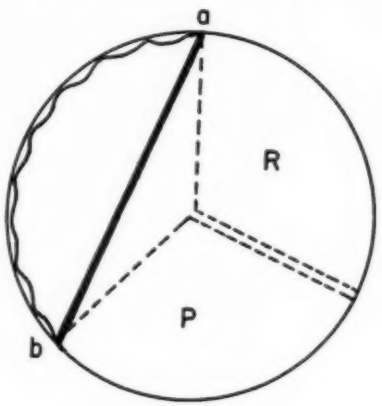

Fig. 4

Fig. 3.—Diagram of the anomaly observed in Case 1. The three cusps were perfectly normal. The elastic band (*ab*) crossed the lumen of the aorta. One of the extremities was attached to the aortic wall, between the posterior and the left cusps. The other between the left and right cusps.

Fig. 4.—Diagram of the anomaly observed in Case 2. The left cusp was absent and in its place there was an elastic band (*ab*) crossing the lumen of the vessel.

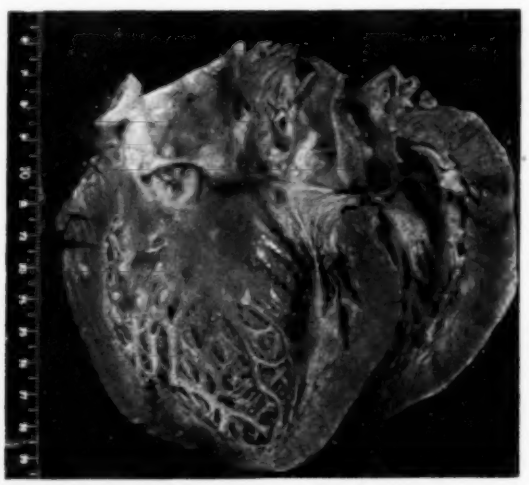

Fig. 5.—(Case 2.) Picture of the heart showing slight dilatation and thickening of the left ventricle thickening of aortic cusps, and the elastic band crossing the aortic orifice.

first hour and 110 mm. in the second (Westergren); examination of the urine revealed albuminuria Grade 3 and creatinine 2.7 mg. per cent. The patient died on March 25, 1950, of congestive heart failure.

Autopsy findings: The transverse diameter of the pericardium measured 14.5 centimeters. The heart showed hypertrophy and slight dilatation. The mitral and tricuspid valves were slightly thickened. The aortic valve showed a great deal of stenosis with only two cusps, the

posterior and the right, both of them extremely thickened. There was a small reddish verrucose lesion on the free border of the posterior cusp. Between the two cusps we found a fibrous band which crossed the long axis of the aortic ring attaching itself to the opposite side of the aortic wall. This band was somewhat elastic measuring 5 mm. in thickness at the extremities and 3 mm. in the central part (Figs. 4 and 5). The diameter of the aortic valve measured 5 cm. There was Grade 2 sclerosis of the aorta. The heart measurements were as follows: tricuspid valve 11.5 cm., pulmonary valve 8 cm., mitral valve 10 cm.; right ventricle thickness 0.4 cm., left ventricle thickness 1.4 cm.; right ventricle depth 7 cm., and left ventricle depth 7.5 cm. The heart weighed 490 grams. There were fibrous adhesions between the lungs and parietal pleurae. The liver showed chronic passive congestion.

On microscopic examination the congenital aortic band was composed, mainly, of elastic tissue arranged in irregular ribbons and bundles. There was a marked inflammatory reaction characterized by fibrosis, slight edema, and cellular infiltration (lymphocytes and monocytes). Few small vessels were observed. An endothelial lining covered the surface of the congenital band. These changes are, in our opinion, similar to those found in the aortic cusps in rheumatic endocarditis.

Autopsy diagnosis: Aortic rheumatic endocarditis, congenital elastic band of aortic valve, absence of the left aortic cusp, dilatation and hypertrophy of the heart and myocardical fibrosis.

COMMENT

The congenital anomalies usually observed in the aortic valve are: absence of one or more cusps, fenestration, changes of the shape, size, and coalescence of the cusps.

It is beyond doubt that we are dealing with a congenital anomaly. In the second case we found besides the congenital band, absence of one of the cusps of the aortic valve. Possibly this anomaly is more frequent than we think. Theoretically the explanation of this anomaly should be as for any malformation of aortic cusps, related to anomalies of the truncus arteriosus. Photographs of the cases were forwarded to Potter and the hearts were personally examined by Taussig; both stated no such anomalies had ever fallen under their observation.

It seems to us that in both cases the congenital anomalies did not contribute to the death of the patients. The murmur heard in the second case, in the aortic area is partly explained by the deformity of the aortic valve brought about by the rheumatic lesion and, possibly also, by the elastic band vibrating during the blood flow. In this case we observed, microscopically, changes on the congenital band similar to those produced by rheumatic fever in the aortic cusps. In both cases sections of the elastic bands have shown, conclusively, the same histological structure of the aortic artery wall.

SUMMARY

The authors report two cases of a congenital aortic valve anomaly, which has not been described previously in the literature. One case was a stillborn boy, the second a 32-year-old white man. In the absence of a better name the authors have called this anomaly, "Congenital elastic band of aortic valve."

REFERENCES

1. Taussig, H. B.: Congenital Malformations of the Heart, New York, 1947, Commonwealth Fund.
2. Blalock, A., and Taussig, H. B.: The Surgical Treatment of Malformations of the Heart in Which There is Pulmonary Stenosis or Pulmonary Atresia, J. A. M. A. **128**:189 1945.
3. Potter, E. L.: Personal communication.
4. Taussig, H. B.: Personal communication.

Book Reviews

INTRODUCTION TO THE INTERPRETATION OF THE ELECTROCARDIOGRAM. By Louis Katz, Richard Langendorf, and Alfred Pick. Chicago, 1952, University of Chicago Press. Price $2.50.

This very short, paper-bound outline of certain elementary aspects of electrocardiography is attractive in appearance and contains many well-selected electrocardiographs illustrating arrhythmias and other deviations from the normal.

However, it does not serve as an adequate introduction to interpretation. It is far too brief for the beginner—too elementary for the advanced student. Perhaps it would serve as a useful outline to a course given by the authors, but it cannot be recommended for any other purpose.

C.W.

CARDIOGRAPHY IN GENERAL PRACTICE. By Abraham I. Schaffer. Baltimore, 1952, Williams & Wilkins Company. Price $3.00.

This small volume of 135 pages consists of a very brief description of three techniques used in the diagnosis of heart disease. These are electrocardiography, vectorcardiography, and ballistocardiography.

Although the book is entitled *Cardiography in General Practice* it is doubtful that the inexperienced reader could get enough from this book to use any of these techniques satisfactorily. It could be useful for those who would like to know in a very general way what these techniques hope to accomplish.

C.W.

MANUAL OF ELECTROCARDIOGRAPHY. By Benjamin F. Smith. New York, 1952, Elsevier Press, Inc. Price $4.50.

Since World War II many texts in electrocardiography have appeared. Most of these are concerned with the simplified explanation of electrical events in cardiac cycle which make it possible to have a rational basis for interpreting patterns. However, so many of these books have appeared that a new one is not worthy of special mention unless it introduces new and more effective ways of explaining basic theory or provides real help in interpretation.

It cannot be stated that this book offers anything beyond that of the standard electrocardiographic text. The latter part of the book is concerned with detailed analysis of electrocardiograms in autopsied cases. This has been done more effectively in other textbooks. The reviewer sees no reason to recommend this book particularly.

C.W.